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TABLE OF CONTENTS

Effect of Medical and Surgical Vagotomy on the Augmented Histamine Test in Man
I. E. GILLESPIE, M.B., F.R.C.S.Ed., and A. W. HAY, M.D., Ch.M., F.R.C.S. 1557
Some Psychiatric Consequences of Gastrectomy F. A. WHITLOCK, M.D., M.R.C.P., D.P.M. 1560
Cytogenetic Studies in Acute Leukaemia A. G. BAIKIE, M.B., M.R.C.P.Ed., PATRICIA A. JACOBS, B.Sc., J. A. MCBRIDE, M.B., M.R.C.P.Ed., and ISHBEL M. TOUGH, B.Sc. 1564
Effect of D-Thyroxine on Serum Cholesterol
RAYMOND GREENE, D.M., F.R.C.P., J. F. PEARCE, M.B., and D. F. RIDEOUT, M.B. 1572
Long-continued Inhibition of Gastric Secretion by Poldine Methosulphate in Patients with Peptic Ulcer
A. H. DOUTHWAITE, M.D., F.R.C.P., T. H. HILLS, M.B., D.M.R.E., and J. N. HUNT, M.D., D.Sc. 1575
Oral Treatment of Pernicious Anaemia with Vitamin-B_{12}-Peptide N. K. SHINTON, M.B., M.R.C.P. 1579
Haemoglobin Q-alpha-Thalassaemia KATHARINE M. DORMANDY, M.B., M.R.C.P., S. P. LOCK, M.B., and H. LEHMANN, M.D., Sc.D., M.R.C.P., F.R.I.C. 1582
ABO Blood Groups of Siblings of Gastric Ulcer and Gastric Carcinoma Patients
JOSEPH A. BUCKWALTER, M.D., and ROBERT E. VAN SCOY 1585

MEDICAL MEMORANDA
Case of Adder-bite with Thrombosis of the Saphenous Vein. G. C. ARNEIL, M.D., Ph.D., F.R.F.P.S., M.R.C.P., D.C.H., and J. C. MACLAURIN, M.B., M.R.C.P.Ed. 1587
A Second Chinese Family with Haemoglobin Q. T. F. DIXON, Ph.D., B.Sc., F.R.I.C., S. PANG, WONG HOCK BOON, F.R.F.P.S., M.R.C.P.Ed., D.C.H., and H. LEHMANN, M.D., Sc.D., M.R.C.P., F.R.I.C. 1588
Spontaneous Delivery of Central Placenta Praevia. JOHN WEEKS, M.B., D.I.H., D.Obst.R.C.O.G. 1589

BOOK REVIEWS 1590

GENERAL ARTICLES AND NEWS
Evolution in the Mental Hospital. A. B. COOPER, M.D., D.P.M., and D. F. EARLY, L.R.C.P.&S.I., D.P.H., D.P.M. 1600
Winchester Address 1603
To-day's Drugs 1603
OBITUARY 1612
MEDICAL NOTES IN PARLIAMENT 1615
VITAL STATISTICS 1617
MEDICAL NEWS 1618
BIRTHS, MARRIAGES, AND DEATHS 1620
QUESTIONS AND COMMENTS 1621

MEDICO-LEGAL
Somnambulistic Homicide 1616

LEADING ARTICLES
N.H.S. in Fuzziland 1594
Normal and Leukaemic Haemopoiesis 1595

ANNOTATIONS
Risks of Hyperventilation before Swimming under Water 1596
Adder Bites 1597
Shortage of Dietitians 1597
Problems of Joint Movement 1598
Protein Requirements in Early Life 1598
Medical Officers in the Armed Forces 1599

CORRESPONDENCE
Shortage of Nurses. WILLIAM N. ROGERS, M.D.; ROGER KYNASTON, M.B. 1604
Settlement of Compensation. J. N. ASTON, F.R.C.S. 1604
Smart Journalism. LOGAN MITCHELL, M.B. 1605
Bilateral Ectopic Pregnancy. J. M. RITCHIE, M.B. 1605

SUPPLEMENT
Full Contents on First Page of Supplement
G.M.S. Committee 269
Agenda of Annual Conference of L.M.C.s 273
Correspondence:
Medical Staffing of Hospitals. L. BELLMAN, M.B., and DUNCAN YUILLE, M.B. 279

CORRESPONDENCE—*contd.*
Ovarian Dermoid Presenting as Ectopic. XTO G. OKOJIE, L.S.M. 1605
Intraperitoneal Haemorrhage from Fibroids. D. J. CANNON, M.D. 1605
Teats. IAN G. WICKES, M.D. 1606
Neonatal Resuscitation. W. C. SPACKMAN, F.R.C.O.G.; W. N. LEAK, M.D. 1606
Plaster Collars for Unilateral Facial Pain. J. CAMPBELL, Ph.D., F.D.S. 1606
Headache and "Eyestrain." DAVID RANKINE, M.B.; THEODORE H. WHITTINGTON, D.O.M.S. 1607
Chronic Headache. N. C. ROLES, M.B. 1607
After-effect of Desert Glare. G. C. PETHER, M.D. 1607
Nitrous Oxide in Dentistry. M. P. COPLANS, F.F.A. R.C.S. 1607
Prevention of Dental Caries. R. A. HOLMAN, M.D. 1608
Autogenous Vaccinia. P. WALSHE, M.B. 1608
Earl of Arran's Blood Alcohol. R. G. BOWLER, B.Sc. 1609
Safety Belts in Cars. A. W. FOWLER, F.R.C.S. 1609
Cardiac Arrest in the Consulting-room. ANDREW C. SMITH, M.B. 1609
Yoga and the Heart. GEORGE X. TRIMBLE, M.D. 1609
Leg Ulcers. J. JACOBS, M.B.; A. G. FERGUSSON, M.D., and J. C. P. LOGAN, M.D. 1609
Letters on other subjects on pp. 1610–11

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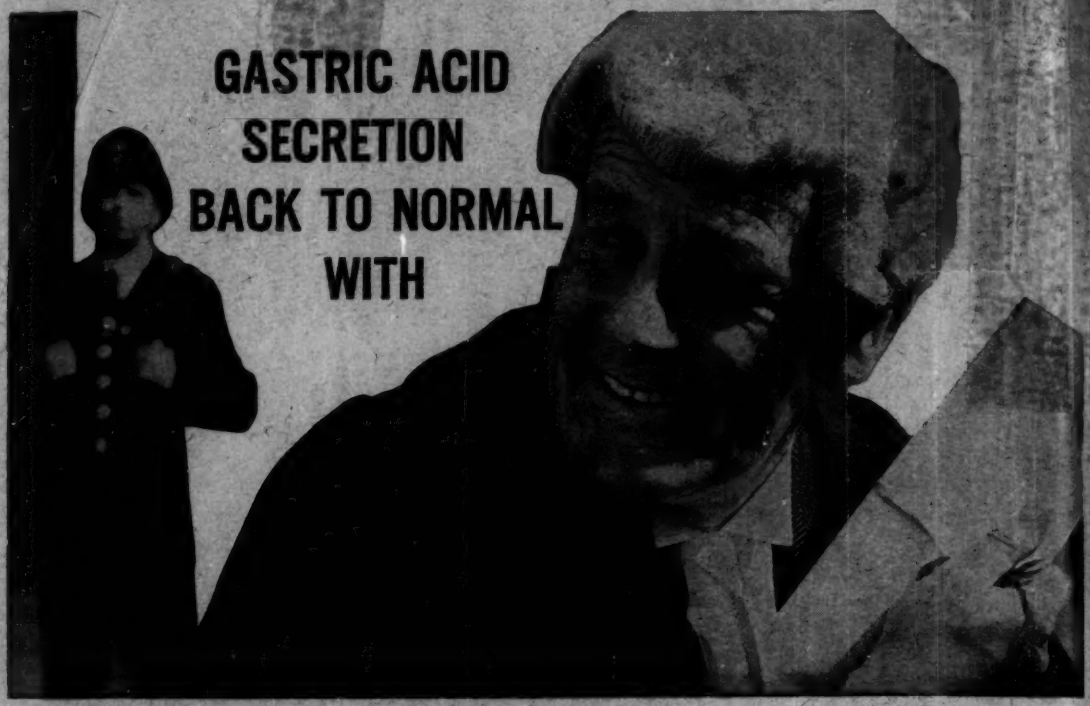

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BRITISH MEDICAL JOURNAL

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EFFECT OF MEDICAL AND SURGICAL VAGOTOMY ON THE AUGMENTED HISTAMINE TEST IN MAN

BY

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When the evolution of surgery in the treatment of duodenal ulcer is traced it is evident that during the last half-century surgeons have directed their efforts along two main channels. Firstly, search has been made for an operation which would cure the existing ulcer and guarantee prevention of recurrent ulceration; new procedures have been numerous and varied, but, after a brief vogue, most have been shown deficient in some respect. Secondly, and more recently, there have been well-planned clinical trials with accurate follow-up results on some of these procedures, in the hope that a particular single operation would be found to be so superior to others as to be suitable for *all* patients with duodenal ulcer. Partial gastrectomy, vagotomy with drainage, and antrectomy with vagotomy are well-tried and useful operations, but each carries a risk of recurrent ulceration and of other unpleasant side-effects. The quest for an ideal operation is now being relinquished in favour of a new objective—the selection of an operation or combination of operations which will most accurately meet the requirements of the individual case. The current studies are directed towards the identification of these requirements.

Surgical vagotomy, which regularly reduces the basal secretion of gastric juice, the nocturnal secretion, insulin-stimulated secretion, and histamine-induced secretion (0.5 mg. of histamine acid phosphate), has also been shown to cause a significant reduction in the maximal histamine secretion as judged by the augmented histamine test (Gillespie, Clark, Kay and Tankel, 1960). This test, preferred to the others on account of its ability to give reproducible results, is routinely used by us to measure the effect of surgical vagotomy on acid gastric secretion.

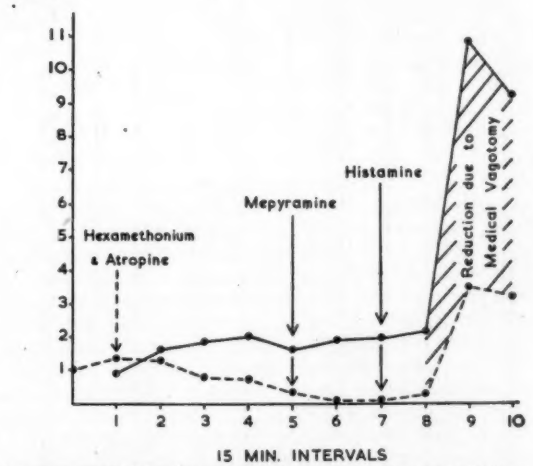
More recently it has been shown that hexamethonium and atropine in combination ("medical vagotomy") is also capable of reducing the augmented histamine response and that a significant correlation exists between this reduction and the reduction due to subsequent surgical vagotomy (McArthur, Tankel, and Kay, 1960). The possible application of these findings to the selection of duodenal ulcer cases suited to vagotomy as surgical treatment was envisaged. In this paper we report the results of such a study.

Methods

All patients included in this study were males with proved duodenal ulcer who had been accepted for surgical treatment. They were selected only in so far that elderly and poor-risk patients were excluded; treatment by gastro-jejunostomy was preferred in these circumstances. A total of 40 patients have been studied. Regardless of the results of the pre-operative acid tests, each was treated by vagotomy with gastro-jejunostomy. The vagal trunks were divided subdiaphragmatically after mobilization of the lower oesophagus, and a posterior gastrojejunostomy was made at the most dependent part of the stomach.

Before operation each patient had two tests: the first was an augmented histamine test; in the second, the effect of medical vagotomy on the augmented histamine test was studied. After operation the augmented histamine test was repeated in all 40 patients.

Medical Vagotomy Modification of the Augmented Histamine Test.—The test is preceded by a 12-hour fast.



An augmented histamine response is represented by the solid line. The effect of medical vagotomy (hexamethonium 50 mg.+atropine 0.325 mg.) is depicted by the interrupted line. The shaded area represents the reduction in "maximal" acid output produced by medical vagotomy.

A No. 16 French gauge "neoplex" gastric tube is introduced through the nose and the fasting contents of the stomach are aspirated by means of an electric suction apparatus. Throughout all subsequent collections, complete aspiration of the gastric juice is ensured by frequently interrupting the suction and injecting a little

air to maintain patency of the tube. A single intramuscular injection of hexamethonium bromide, 50 mg., with atropine sulphate, 0.325 mg., is followed by the collection of four 15-minute total aspirates. The fourth specimen usually reveals absence of free hydrochloric acid. An antihistamine (100 mg. of mepyramine maleate) is now given intramuscularly and followed in 30 minutes by a subcutaneous injection of histamine acid phosphate, 0.04 mg./kg. body weight. A further three 15-minute aspirates are then collected as in the standard augmented histamine test (Kay, 1953). All 15-minute aspirates are measured for volume, *p*H, and free hydrochloric acid output by titration with N/10 sodium hydroxide, using Topfer's indicator. Comparison of the acid output in the last two 15-minute aspirates in the standard augmented histamine test and in the test after medical vagotomy represents the effect of medical vagotomy on the augmented histamine response (see Chart on previous page).

Mild postural hypotension, the only side-effect observed commonly during the medical vagotomy test, was controlled by keeping the patients recumbent for about two hours after the test.

Results

Effect of Surgical Vagotomy.—The effect of surgical vagotomy on the augmented histamine response in the series of 40 patients is shown in Table I. The average reduction obtained was 58.5%.

TABLE I.—*Effect of Medical and Surgical Vagotomy on the Augmented Histamine Response. Acid Outputs in mEq in 30 Minutes*

Case No.	Before Vagotomy	After Medical Vagotomy	% Reduction	After Surgical Vagotomy	% Reduction
1	23·6	13·6	43	6·3	73
2	17·7	10·5	41	6·5	64
3	18·1	11·0	40	6·4	65
4	21·6	14·4	33	4·5	79
5	16·1	8·5	47	5·0	69
6	10·6	7·5	29	5·3	50
7	17·3	14·5	16	11·8	32
8	16·1	8·9	45	9·1	44
9	28·6	15·7	45	17·7	38
10	30·7	13·5	56	6·8	78
11	14·0	7·6	46	2·0	85
12	21·9	13·4	39	8·1	63
13	23·0	13·5	41	7·7	67
14	16·6	11·3	32	0	100
15	21·9	16·5	25	9·9	55
16	13·1	9·1	31	7·2	45
17	18·7	13·1	30	7·6	60
18	12·2	5·5	55	1·3	89
19	17·6	11·6	34	12·1	32
20	26·5	13·6	49	11·8	56
21	16·6	9·0	46	9·8	41
22	12·8	10·0	21	9·0	29
23	21·7	9·1	58	4·1	81
24	23·0	6·4	72	8·3	64
25	20·0	6·7	67	10 4	48
26	17·8	10·3	42	7·5	58
27	7·2	0·4	95	4·2	41
28	12·9	10·6	18	6·7	49
29	17·3	14·6	16	13·8	20
30	21·4	8·2	62	6·4	70
31	22·7	19·5	14	9·6	58
32	12·7	10·5	17	7·8	38
33	39·2	17·7	55	31·1	21
34	17·3	5·7	67	5·1	71
35	15·2	14·1	8	9·4	39
36	9·9	0·1	99	2·0	79
37	19·8	11·1	44	3·4	83
38	23·6	10·1	57	5·7	76
39	10·2	6·1	40	3·8	63
40	16·0	9·4	41	5·1	68
Average % reduction					58·5

Comparison of Pre-operative Medical Vagotomy and Surgical Vagotomy

The acid outputs obtained after the medical vagotomy modification of the augmented histamine test, and the percentage reductions of these on the standard augmented histamine tests, are also shown in Table I.

Prior to detailed consideration of these results, attention is directed to technical defects in the performance of the investigation in four patients. In Case 27 blood was present in the pre-operative medical vagotomy tests, and collection difficulties were encountered in the pre-operative medical vagotomy tests in Cases 35 and 36. Case 33 would appear to have had an incomplete surgical vagotomy, as a much greater reduction in the augmented histamine response occurred after medical vagotomy (55%) than after operation (21%); a discrepancy of this order was not encountered in any other case. Incomplete vagotomy has since been confirmed by the results of secretion studies after transthoracic vagotomy.

For the reasons given, these four cases have been excluded from the subsequent analysis. There is good correlation between the effect of medical and surgical vagotomy on the augmented histamine response in the remaining 36 cases ($r=0.4783$, $t=3.176$, $P<0.01$). The reduction after surgical vagotomy was generally greater than that following hexamethonium and atropine; this is due largely to the effect of the gastro-jejunostomy stoma (McArthur *et al.*, 1960).

Table I shows that, although in most cases reductions in the augmented histamine response of more than 50% occur after surgical vagotomy, there are five in which the reductions are less than 35% (Cases 7, 19, 22, 29, and 33). In one of these five (Case 33) vagal section was incomplete. The other four show reasonable agreement between the two reductions, indicating that surgical vagotomy was complete. The mean percentage reduction of the augmented histamine response after surgical vagotomy in this group of four is *28.3*%, with a standard deviation of 4.9%, whereas that of the remaining 35 patients is *63.1*%, with a standard deviation of 15.8%. Although there is no valid mathematical support for a separation, these figures must suggest that duodenal ulcer patients may be divided into two groups as regards the effect of surgical vagotomy on acid production. This is discussed later.

The period of clinical follow-up ranges from six months to four years. To date, two patients in the present series have developed recurrent ulceration. In the first (Case 33) acid secretion tests had indicated incomplete vagotomy, and the recurrence was treated by transthoracic vagotomy to ensure division of all vagal fibres. The other recurrence appeared within four months of vagotomy in Case 29, one of the four with a small reduction of the augmented histamine response (20%); evidence of complete nerve section is provided by the failure of the post-operative medical vagotomy test to effect a further significant reduction (Table II).

TABLE II.—*Summary of Secretion Studies in Case* 29

	Augmented Histamine Response. Acid Output in mEq in 30 Minutes	% Reduction of Pre-operative Augmented Histamine Response
Before vagotomy ..	17·3	—
After medical vagotomy	14·6	16
,, surgical vagotomy	13·8	20
Post-operative medical vagotomy	12·1	30
A.H.R. at 4 months (stomal ulcer) ..	15·5	10
After antrectomy ..	2·1	88

At the operation for the recurrent ulcer it was decided to ablate the chemical phase of secretion rather than carry out subtotal resection. Antrectomy was performed, histological confirmation being obtained that the antrum alone had been excised. Thus, in tests after

this second operation, the original population of parietal cells was still available for stimulation. These tests showed that the reduction of the augmented histamine response had now increased to 88%. The acid responses in this patient before and after his two operations are summarized in Table II.

Discussion

The results of acid-secretion studies in this series of 40 duodenal ulcer patients confirm that vagotomy reduces the acid output of the stomach in response to the augmented histamine test. Inspection of the reductions effected by surgical vagotomy shows that the majority were greater than 50%, that there was a wide variation in individual results, and that small reductions occurred in a few patients. A figure of 35% reduction in the augmented histamine response has been chosen arbitrarily to divide the series into two groups: 35 patients had a reduction of more than 35% (group A) and 5 had a reduction of less than 35% (group B). Extension of the series will be required if a critical level is to be established by statistical means. However, scrutiny of data relating to the effect of vagotomy on the augmented histamine test by other workers (Janowitz, 1961; Kyle, 1961, personal communication) shows that they too found a few patients with a remarkably small reduction after operation.

As in the present investigation, Janowitz and Kyle had been careful to perform special studies on their patients which provided good evidence that the surgical vagotomy had been complete. Consequently, the possibility has to be envisaged that the vagus nerves, while dominating the control of acid secretion in most cases of duodenal ulcer, may exert only a minor influence in some cases. In this minority, the antral (hormonal) influence may dominate, and these patients would seem to be unsuited for surgical vagotomy as the treatment of duodenal ulceration. If this finding is confirmed, it will become important in practice to identify such patients before selecting the appropriate surgical operation for the treatment of their duodenal ulceration. This hypothesis should be the subject of further study.

Statistical analysis of the overall series of 40 patients shows that the results of the medical vagotomy described in this paper correlate satisfactorily with the results of subsequent surgical vagotomy. In particular, a small reduction in the augmented histamine acid response was predicted in all four patients in group B in whom subsequent complete surgical vagotomy effected the same small reduction. It is of particular interest that one of these four (Case 29) has already reported with symptoms of recurrent ulceration; the only other recurrence in the series so far has been in the patient shown to have an incomplete vagotomy (Case 33). At reoperation on Case 29 it was decided to perform antrectomy alone rather than subtotal gastrectomy (the usual operation in cases of stomal ulceration), thus ablating the chemical production of acid secretion without reducing the number of acid-secreting cells. Subsequent tests in this patient showed that the augmented histamine response had now been reduced by almost 90% from the original level. In this patient the antral phase, and not the vagal phase, would seem to have been the predominant cause of his acid hypersecretion—as had been predicted by the results of the medical vagotomy tests.

Although these tests predicted that surgical vagotomy would effect a small reduction in the augmented histamine response in four patients, a similar small reduction from medical vagotomy was associated with a much larger reduction after surgical vagotomy in six others (Cases 6, 15, 17, 28, 31, and 32). The results of the pre-operative tests in these patients would have led to their classification as unsuited to surgical vagotomy; antrectomy with vagotomy or partial gastrectomy would have been preferred. It should be noted, however, that the error of the test was in this direction only, and the net result would mean that a few patients in group A would be subjected to antrectomy with vagotomy as opposed to vagotomy with a simple drainage procedure. The results in these patients, which merit careful consideration, raise the question of whether there are defects in the test which can be overcome. Two of the six patients having anomalous results (Cases 28 and 32) were obese, and it is possible that the dose of hexamethonium and atropine was inadequate to produce complete medical blockade. The possibility that a body-weight dose-curve exists for hexamethonium–atropine combination is at present under consideration. Again, the timing of the hexamethonium plus atropine injection described in this paper may permit the effect of medical vagotomy to wane during the period of maximal histamine stimulation; studies are in progress concerning this point.

The major considerations in selecting an operation which will most accurately meet the requirements of the individual case include the immediate mortality and the risk of recurrent peptic ulceration. The following figures have been taken from a recent review of the surgical treatment of peptic ulcer by Welbourn and Johnston (1961). Subtotal gastrectomy has an immediate mortality of 3.7%, with a recurrent ulcer rate of 1.4%; this mortality can be attributed largely to the necessary dissection in the neighbourhood of the duodenal ulcer and the technical difficulties of closing the duodenal stump. Vagotomy with a drainage procedure has an immediate mortality of 0.6% and a recurrent ulcer rate of 1.8%; it should be noted that the average follow-up period of this operation is about 10 years, and a more accurate recurrent ulcer rate cannot be determined until the results of a full 20-year follow-up period are available for study.

Vagotomy with antrectomy is theoretically the most physiological procedure, as it removes both the nervous and the hormonal phases of acid gastric secretion. The immediate mortality from this procedure is 2.6%, with a recurrent ulcer rate at five-year follow-up of 0.4%. This combination of operations probably offers the best protection against recurrent ulceration, but by reintroducing the hazards of closure of the duodenal stump the immediate mortality is greater than that associated with simple vagotomy. Again, while the actual reduction in gastric capacity produced by removal of the antrum is not great, the rate of gastric emptying may be increased (particularly when a gastro-jejunal anastomosis is made), thus reducing the effective capacity of the stomach; accordingly, the "small stomach" syndrome may again be a sequel to this operation just as it has been the main cause of poor results from subtotal gastrectomy. It can be concluded that vagotomy without gastric resection is the safest of these three acceptable operations.

On the basis of the present study a surgical policy for the surgical treatment of duodenal ulcer can be formulated. Before operation an augmented histamine test is done (A=the acid output in mEq) and the effect of medical vagotomy on the augmented histamine test

is also estimated (B=the acid output in mEq). The percentage reduction of the augmented histamine response obtained from medical vagotomy (C) is readily obtained thus:

$$C=\frac{A-B}{A}\times 100$$

Where C is greater than 35%, vagotomy with a drainage procedure is selected as the surgical procedure; where C is less than 35% vagotomy with antrectomy is preferred.

This policy ensures that the majority of patients will be treated by the simplest and safest operation and also ensures that patients in whom vagotomy can be expected to give but a poor reduction in acid secretion will be given the greater guarantee from recurrent ulceration which is afforded by the combined procedure of antrectomy with vagotomy.

The main endeavour of the gastric surgeon to-day is to reduce the proportion of patients in whom the result is unsatisfactory. This will not be achieved by the adoption of any one standard operation, but by the clear definition of the situations in which each procedure is likely to be most effective. The hypothesis proposed in this paper provides a physiological basis for recurrent ulcer in a proportion of cases. It is important that the hypothesis, and the pre-vagotomy test which has stemmed from it, be subjected to further study.

Summary

The effect of hexamethonium and atropine (medical vagotomy) on the augmented histamine response has been studied in 40 duodenal ulcer patients with a view to predicting the effect of surgical vagotomy on this response. Good correlation exists between the reductions from medical and surgical vagotomy.

The medical vagotomy test picked out four patients who had a small reduction, and a similar reduction was found in these cases after surgical vagotomy. On this basis, a hypothesis has been formulated that duodenal ulcer patients may be divided into two groups: in the majority the nervous control of acid secretion appears to be dominant; a minority group with antral dominance would seem unsuited for surgical vagotomy and the medical vagotomy modification of the augmented histamine test described in this paper may be of value in selecting patients belonging to this group.

We thank Mr. J. McArthur, of Dumfries and Galloway, Royal Infirmary, for some of the earlier results in this series, and Mr. D. Kerridge, of the department of statistics, University of Sheffield, for helpful advice in the interpretation of the results.

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The Atomic Energy Authority and the National Institute for Research in Nuclear Science have agreed that the development of particle accelerators hitherto carried out by the Accelerator Division, A.E.R.E., Harwell, should be the responsibility of the Rutherford Laboratory of the National Institute for Research in Nuclear Science.

SOME PSYCHIATRIC CONSEQUENCES OF GASTRECTOMY

BY

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Mental disturbances after surgical operation are fairly frequent and in most cases short-lived. Their clinical characteristics have been described in a number of papers under the heading of post-operative psychoses which are well recognized by surgeon and psychiatrist alike. Whereas the acute post-operative psychosis is fairly well documented less is known about the long-term effects upon the psyche of surgery. As Navratil (1959) points out, follow-up studies of surgical cases are usually carried out by surgeons, who are less likely to ask specifically about neurotic and personality disorders than are their psychiatric colleagues. An acute psychosis in the ward immediately after an operation cannot be ignored. Neurotic symptoms of fairly severe degree can be missed at a follow-up clinic unless specific questions are asked to elicit them.

Compared with most of his colleagues the psychiatrist sees a not inconsiderable number of patients who date their symptoms from the time of an operation. The woman who develops an intractable neurotic illness after a hysterectomy is a fairly familiar figure in the psychiatric out-patient department. Surprisingly little has been written on the psychiatric sequelae of partial gastrectomy and other surgical procedures for the relief of peptic ulcer, although European workers seem more familiar with the problem—particularly when alcoholism is concerned—than do their American and British colleagues. It was a chance observation of patients who had become chronic alcoholics after a partial gastrectomy that led to a further examination of a number who had been admitted to the psychiatric wards at some time after this operation.

Results

In all, 25 patients were examined (17 men and 8 women). At the time of their first admission to a psychiatric ward the men's ages ranged from 28 to 60 years, with a mean of 46, while the ages of the women varied from 37 to 55, with a mean of 47. Of the 17 men, nine were admitted directly or indirectly because of alcoholism, two for treatment of drug addiction, and the remaining six for mixed neurotic and depressive states. Three of the women were drug addicts, and the remainder had mixed depressive and anxiety symptoms. All except one of the women had been operated on for duodenal ulceration, and all except two of the men who had gastric ulcers were similarly affected. Only two of the women appeared to be in a good nutritional state, and all except four of the men were thin and underweight. Almost all the patients complained bitterly of severe dumping symptoms. The alcoholics and four of the drug addicts all said that their drug relieved these symptoms.

It was difficult to obtain a clear picture of the premorbid personalities of these patients, and only the most general features emerged. Judging by work record, by absence of overt psychiatric illness, and by the general level of social adaptation, three of the male alcoholics had been normal up to the time of operation, five had

shown psychopathic features, and one had a former neurotic breakdown. Both the addicts had managed well up to the operation. All except one of the men affected by mixed anxiety and depressive symptoms had appeared normal prior to operation. Of the female addicts, one was normal, one was psychopathic, and one was neurotic before their partial gastrectomy. Three of those admitted with anxiety and depressive symptoms had managed well before operation, whereas two had had previous neurotic breakdowns. When it was possible the premorbid personality was checked by a history obtained from a relative, but it was not possible to do this in all cases. Of the nine alcoholics, five had been moderate and four heavy drinkers before operation. Despite this, their drinking had not been of such intensity as to warrant their seeking medical advice, and they had been able to carry on at work.

Since the time of their first psychiatric admission three of the patients had died, two being male alcoholics and the other a woman suffering from a variety of psychosomatic disorders and depressive symptoms. This patient, who had already made one suicidal attempt with barbiturates, eventually succeeded in ending her life with these drugs. The two alcoholics died as a direct result of their drinking, one accidentally suffering fatal burns while in an alcoholic stupor, the other from liver failure and bronchopneumonia.

The following abbreviated case-histories of some of the patients indicate the nature of the problem and its relationship to the treatment of their peptic ulcers.

Male Cases

Case 1.—A married salesman aged 58 was admitted to hospital for treatment of alcoholism. He developed symptoms of duodenal ulcer at the age of 28. Between the onset and his partial gastrectomy at 48 he perforated on two occasions. Although he drank fairly heavily at about the age of 25, his wife confirmed that he drank only moderately until after his partial gastrectomy. He had worked well and had advanced to a position of some responsibility in his firm. There was evidence to suggest some degree of sexual impotence at different times during his marriage; but he had one son, and his wife spoke well of him as a likable and reasonable man until the age of 48. Since then he has suffered severely from dumping symptoms, claiming that beer and cider relieve these. When admitted he was an obvious chronic alcoholic, and, although there was some preservation of his self-respect, he was untruthful and unreliable. He refused treatment for his drinking, but eventually returned and was placed on disulfiram with success. However, he relapsed, and for the past six weeks had been drinking very heavily again and refusing all offers of help.

Case 2.—A married labourer aged 38 was admitted to hospital after an attempt at suicide with barbiturates while intoxicated with alcohol. Symptoms of duodenal ulcer had developed at the age of 20. Partial gastrectomy was performed at 29. He first married in 1938, when aged 18, but the marriage broke up during the war, and he obtained a divorce at the age of 26. He remarried shortly afterwards. He had had a number of unskilled labouring jobs but had not been unemployed except for medical reasons until after his gastrectomy. Since then his work record had gradually deteriorated, and he had done little work in the year prior to admission. Before operation he had been a moderate drinker—a fact confirmed by his wife—but since operation he had complained of dumping symptoms, and drank heavily to relieve them. He said that before operation he had to limit his drinking as his ulcer would become active if he over-indulged. Since operation he had also been resorting to barbiturates in increasing dosage to combat insomnia and depression. Between admission and the time of his death he was readmitted twice, both after suicidal acts while intoxicated. One such act was precipitated because of a charge for breaking open a gas-meter to obtain money for more alcohol. He was placed on probation, but despite continued treatment he went on drinking. Eventually his wife left him, and he was discovered dead in his house, having accidentally set himself on fire with a cigarette when in an alcoholic stupor.

Case 10.—A married coal-miner aged 39 was admitted for treatment of addiction to phenadoxone hydrochloride. He developed symptoms of duodenal ulcer at the age of 23 while in the Army. Ten years later a partial gastrectomy was followed by severe dumping symptoms. He was given phenadoxone, and he discovered that this relieved his symptoms. In the years after his operation he became addicted to this drug, requiring up to eight 10-mg. tablets daily. He also drank moderately, as he found that alcohol relieved his symptoms. He had not required psychiatric treatment before his operation and his work record was reasonably good.

Case 11.—A married fishmonger aged 53 was admitted for treatment of morphine addiction. Duodenal ulcer symptoms started at the age of 33, and he had a vagotomy at 41 followed by a partial gastrectomy two years later. Before his vagotomy he had been given morphine occasionally, but since his gastrectomy he had been requiring up to four ½-gr. (32-mg.) tablets of morphine sulphate a day. He was unable to manage without this dose, but it was possible to admit him and treat him successfully. He seemed to have managed his business well, and there was no clear evidence of personality disturbance before his operation. He drank moderately because he believed it was good for his stomach. Despite the operation he had an active gastric ulcer which was causing symptoms.

Case 12.—A married labourer aged 31 was admitted for treatment of phobic anxiety and depressive symptoms. At the age of 20 he developed symptoms of peptic ulceration, and he had a partial gastrectomy at 27. He was found to have a gastric ulcer. After his operation he developed severe dumping symptoms, and became tense, morose, and anxious. According to his wife he had always been a cheerful man until his operation, since when he had been constantly depressed and had lost a lot of work. He drank beer in moderation, as he found this relieved his depression. At no time had he been a heavy drinker. There was no clear evidence of neurotic personality traits during childhood and adolescence. His work record was good and his marriage stable and satisfactory.

Case 13.—A married sales-representative aged 44 was admitted for symptoms of fatigue and depression. Gastric ulcer symptoms began at the age of 35, and he had a partial gastrectomy at 41. Before operation he had worked himself into a position of executive responsibility, but since then had lost confidence in his ability, and had had to take a more humble post. To use his own words, "I hadn't the stomach for the job." He complained of dumping symptoms, was depressed, wept easily, and had lost weight. Because of his symptoms he had lost a lot of time off work, whereas formerly he had rarely been off for reasons of ill-health. There was no clear evidence of neurotic illness in the past, and although he had shown certain obsessional personality traits he seemed to have managed his life successfully up to the time of operation.

Female Cases

Case 18.—A housewife aged 46 was admitted to hospital for what was regarded as an agitated depression complicated by auditory hallucinations. There was much evidence to suggest that she had been taking "drinamyl" in steadily increasing doses and that this was responsible, in part, for her symptoms. She had been in hospital for treatment of depression at the age of 36. Duodenal ulcer symptoms started at 34, and she had a partial gastrectomy following a perforation at 40. After operation she complained of

dumping symptoms, and used drinamyl by day and barbiturate sedatives at night to counter these. For four months before her second admission at the age of 46 she had been becoming increasingly depressed and agitated. Her hallucinatory symptoms subsided soon after admission, when all drugs were withheld. She had always been an anxious person, but seemed to have managed her marriage and two children with success.

Case 19.—A housewife aged 40 was first referred at the age of 37 after a partial gastrectomy for duodenal ulcers one year before. Since her operation she had experienced severe dumping symptoms, for which she consumed large quantities of bismuth and kaolin mixtures containing tincture of chloroform and morphine. She admitted to taking 1½ to 2 bottles each day, and it was reckoned that she was receiving between ¼ and ½ gr. (30 and 20 mg.) of morphine each day. She had married at the age of 19 and had three children. The marriage had not been a happy one, and the husband was unreliable and violent. There was no clear evidence of psychopathy or neurotic disturbance in the patient before her operation. Since then she has lost weight, complained of vomiting, loss of sleep, depression, and fatigue. She claimed that the gastric sedative mixtures alone helped her to continue.

Case 20.—A housewife aged 31 was admitted for treatment of addiction to a patent preparation containing carbromal. She was treated for a duodenal ulcer by partial gastrectomy at the age of 26. Her ulcer symptoms are said to have started at 17, but there is reason to believe that this is not true. Throughout her life she has exhibited features of psychopathic behaviour, and it was difficult to rely on her history. Her husband said that she started taking drugs about one year after her operation when she was depressed. For this reason he left his work in the south and moved north for the patient to be near her own family. After a suicidal attempt at the age of 30 she was admitted for treatment of mixed depressive-anxiety symptoms. Since then she admitted to always requiring a sedative at night, and that she sometimes took it by day as well. She appeared to be receiving thalidomide from her practitioner.

Case 21.—A widow aged 51 was admitted for treatment of depression. Peptic ulcer symptoms began at the age of 33, and she had a partial gastrectomy for a duodenal ulcer at 43. Her husband was killed in the war in 1942, and since then she had continued at work to bring up her two children. After her gastrectomy she had not worked, had felt miserable, and had complained bitterly of dumping symptoms. For the past eight years she had required regular night sedation, had lost weight, and had been admitted on a number of occasions for treatment of her post-gastrectomy syndrome. On admission she was thin, looked older than her stated age, and was depressed and anxious.

Case 23.—A widow aged 59 was first admitted after a suicidal attempt at the age of 54. Duodenal ulcer developed at the age of 42, and was treated by partial gastrectomy at 51. She married when aged 21, had two children, and her husband died when she was 48. Throughout her life she had indifferent health. A hysterectomy was performed at the age of 34 and a nephrectomy at 42. She had not come under psychiatric care until her suicidal attempt when aged 54. After her gastrectomy she became depressed and solitary. She also developed attacks of asthma. Between 1955 and 1958 she continued to attend the psychiatric out-patient department intermittently. She was readmitted in 1958 and again in 1960 for depression. After her last admission she was seen as an out-patient, continued to complain of anxiety and depressive symptoms, and finally committed suicide by taking an overdose of barbiturates.

Discussion

These brief case histories serve to indicate the general nature of the problem. Quite obviously, from a total of 25 cases it would not be possible to derive statistical information which can be related to the general problem of post-gastrectomy syndromes. Nevertheless, certain facts emerge.

The outstanding feature is the high incidence—56%—of alcoholism and drug addiction in this small series. To some extent this could be explained on the grounds that alcoholism and drug addiction are frequent causes of admission to psychiatric wards. On the other hand, so are symptoms of depression and anxiety. Consequently it seems remarkably unlikely that the 56% incidence of alcoholism and drug addiction can be explained on a basis of selection. In any case, there are reasons to believe that the association between partial gastrectomy and these two addictions is not a chance one.

Review of the Literature

Hagnell and Wretmark (1957) quote Engest's observation that of 419 alcoholics 17.7% had had a peptic ulcer, compared with an incidence of 12.8% in the general population. 31% of cases had had a partial gastrectomy, compared with 12% among non-alcoholic cases of peptic ulcer. In their own series of 130 male alcoholics 18.5% of cases had had a peptic ulcer, compared with 8.1% in their controls. Of the alcoholic peptic ulcer cases 29.2% had had a partial gastrectomy, and over half their alcoholics with peptic ulceration had their ulcers before they developed alcoholism. The D.U./G.U. ratio was 7:1 among the alcoholics, compared with 2.3:1 in the non-alcoholics.

Lereboullet *et al.* (1955) note that partial gastrectomy for duodenal ulcer was four times as frequent among alcoholics as among non-alcoholics. In about half their cases the addiction started between three months and five years after operation. Martimor *et al.* (1956) found partial gastrectomy four times more common among hospitalized alcoholics than among those suffering from other mental disorders. Delore and Chaupy (1956) observed 13 men requiring treatment for alcoholism after partial gastrectomy, but felt that the association was a chance one. Levrat *et al.* (1958) comment on the bad operational risks where alcoholism and peptic ulceration coincide.

Navratil and Wenger (1955) found that 24.5% of 200 male alcoholics had a peptic ulcer and that 19% had had a partial gastrectomy. Soeder (1957) feels that there is a special tendency for gastrectomized patients to develop alcoholism, instancing 14 cases of his own, all of whom came into his class of neurotic drinkers who drank to relieve their symptoms.

Dick *et al.* (1959) review a number of papers on alcoholism and gastrectomy in which the incidence of post-operative alcoholism varies from 5.4 to 70%. From their own experience they did not feel that the risk of causing alcoholism by partial gastrectomy was sufficient to deter them from continuing with the operation. In a further paper, Navratil (1959) criticizes the report of Dick *et al.*, going on to summarize the findings in 500 patients with alcoholism, of whom 103 became so afflicted after partial gastrectomy.

Little attention has been paid to this matter by English and American workers. Kapp *et al.* (1947) studied a small group of men who had had psychiatric breakdowns associated with peptic ulceration, and comment on eight cases of alcoholism. None of their cases had been treated surgically. Browning and Houseworth (1953) examined the effect of surgery on 30 patients with duodenal ulcer, compared with the same number treated

medically. No specific mention of alcoholism is made, but they noted a 50% increase of psychoneurotic symptoms in their gastrectomized patients.

In a brief note Poloni (1953) observes that one-tenth of a series of partial gastrectomies became severe alcoholics.

Relation Between Gastrectomy and Alcoholism

From this brief summary of the literature there seems to be evidence to indicate that partial gastrectomy bears a causative relationship in a proportion of cases to subsequent alcoholism, drug addiction, and psychoneurotic illness. Opinions differ over the nature of this relationship. It is the question of alcoholism and partial gastrectomy which appears to have attracted most attention in the past, and, contrary to what might be expected, the peptic ulceration is often present before heavy drinking has become a problem. There is not much reason to believe that alcoholism is a direct cause of ulceration, although it is a fruitful cause of chronic gastritis. After a partial gastrectomy the speed of absorption of alcohol into the blood-stream increases. Because alcohol is a drug of addiction it is arguable that repeated exposure of the brain tissues to intoxicating doses increases the craving for more. This might be the explanation in a proportion of cases, but it is doubtful if it is the whole explanation. A number of patients continue to drink in moderation after a partial gastrectomy, and, whether or not they have other psychiatric symptoms, they do not become chronic alcoholics.

A matter of greater importance is the attitude of the patient to dumping symptoms. This is a common post-operative complication, and all the alcoholics said that they drank to relieve these symptoms and the depression brought on by their uncomfortable physical state. Intoxicated, their spirits rose, only to sink lower as the effect of drink wore off. Similar considerations apply to four of the five drug addicts who used their chosen anodyne to relieve them of the symptoms of the post-gastrectomy syndrome. However, the fact that the effect of dumping symptoms is not the whole explanation was made clear by a patient—not in this series—who attempted suicide shortly after a partial gastrectomy. When seen six months later he was cheerful and well. He admitted to having dumping symptoms which did not upset him greatly. He enjoyed his meals, and took alcohol in moderation. He denied vigorously that the after-effects of gastrectomy had anything to do with his suicide attempt, which was precipitated by anxiety lest a minor fraud he had committed should be discovered. Once this matter was put right he regained his spirits and returned to work.

There is evidence to suggest that the personality of the sufferer from duodenal ulceration differs from that of one afflicted with a gastric ulcer. In this series all the alcoholics and drug addicts had had their partial gastrectomy for relief of duodenal ulcer symptoms. On theoretical grounds one might assume that those suffering from duodenal ulcers had unconscious conflicts of an oral nature which, given a change of circumstances, could be expressed through alcoholism and addiction to a drug. The absence of any satisfactory information about the premorbid personality of these patients makes it difficult to test this hypothesis, but the high correlation of alcoholism and drug addiction in this group of post-gastrectomized patients with a pre-existing duodenal ulcer makes it at least a possible or partial explanation.

A further concept adds point to this theory. It is often stated that psychosomatic illness can in some way protect a patient from a more serious underlying psychotic breakdown if the psychosomatic symptoms are relieved. The evidence for or against this idea has been debated for some years. If it is correct it would account for the consequences of gastrectomy in this series of patients. Whatever else might be said about their illnesses there seems to be little doubt that their social adjustment when they had peptic ulceration was greatly to be preferred to the state of affairs existing after operation. Among the alcoholics it did seem that an existing ulcer acted as an efficient brake on excessive drinking. Alternatively, it gave them an escape route when their normal, but possibly precarious, adjustment was threatened. The ulcer pain became more active, they had to stop work, go on a diet, stop drinking, or even go to bed.

Once the ulcer was removed they had no further pain. Instead they had dumping symptoms which added to their discomfort, leading to increasing consumption of alcohol or drugs for relief. The ulcer no longer acted either as a brake or as a safety-valve. As an intelligent alcoholic commented, "Once I had my operation I no longer got a hangover, and I could go on drinking the next day without trouble." This admittedly was not the usual experience of these patients, but they all commented on the relief they obtained from drinking. Although they implied that it was dumping symptoms for which they sought relief it appeared that the depression and anxiety was of greater concern to them. No longer having an active ulcer, drink or drugs was their only way of escape. As is so often the case, the novelist has made his own independent observations before the psychiatrist:

> "A fresh tray of drinks was thrust in his hands. 'Stiff ones,' Leslie whispered fierce in his ear; 'they've had a couple of rounds of water, this'll put some gyp into things.' But then his ulcer rose to help him, the pain hit so suddenly he could only push the tray back into Leslie's hands. It often discovered its own escape route this way."—William Plomer, *The Loving Eye*.

The fact that there were no alcoholics among the women can possibly be explained by cultural factors. Addiction in three cases to narcotic drugs is probably fortuitous in that these drugs were prescribed for relief of pain. If, however, there is a special tendency for some post-gastrectomized patients to become addicted it is plainly desirable that such drugs should be prescribed with caution. Once the habit was formed the unpleasant withdrawal effects made it very difficult for the patient to give up the drug unaided.

How far the occurrence of psychoneurotic symptoms in this series is coincidental rather than causally related to the operation is not easy to say. Certainly in some cases there was an abrupt change in behaviour pattern indicated by the development of intractable depressive and anxiety symptoms in a person who up to the time of operation had been functioning with reasonable efficiency. However, it would be hard to make out a case for the suggestion that the gastrectomy was a specific cause of the breakdown in the same way as seems likely in the cases of alcohol and drug addiction. In all probability the operation came as a particularly stressful experience to a vulnerable personality who thenceforth was unable to cope with the additional burden of post-operative symptoms.

It is not easy to see what should be done to prevent symptoms of the kind described in this paper. Faced by a patient with a duodenal ulcer who is known to be a moderate drinker and who has had a number of acute complications of his ulcer, the surgeon must choose whether or not to operate. If he does not do so he may endanger the life of his patient. If he carries out a partial gastrectomy he might convert a reasonably adjusted individual into a chronic alcoholic, incapable of work, a burden to himself and his family alike. A warning about the possible effects of drinking after operation should be given, and if the patient is obviously drinking to excess he should be referred for psychiatric help. Undue preoccupation with dumping symptoms, persistent loss of or failure to regain weight, and repeated requests for potentially habit-forming drugs should all be regarded as warning signals indicating that the patient might be heading for a breakdown or addiction.

In the absence of any clearly defined pattern of behaviour or of personality it is not easy to avoid operating on those who might thereby be exposed to a special risk of breakdown. Those who show psychopathic features or who are prone to resort to drink to relieve their anxieties should be detected before operation so that psychiatric treatment can be started before and continued after operation. By doing this one might hope to avoid some of the unfortunate consequences of partial gastrectomy described in this paper.

Summary

25 patients (17 men and 8 women) were admitted for psychiatric treatment after a partial gastrectomy. In most cases this was done for relief of symptoms of duodenal ulcer. 56% of these cases were admitted for treatment of alcoholism or drug addiction. A review of previous work suggests that there is a special relationship between the operation and subsequent addiction to alcohol and drugs. This special relationship may not hold when psychoneurotic illness follows partial gastrectomy. In such cases the operation probably acts as a non-specific stress in a vulnerable personality.

The implications of these findings are discussed, and it is suggested that the development of certain symptoms post-operatively may indicate the need for psychiatric treatment.

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Copies of *The Prevention of Accidents in Childhood*, a report of a seminar sponsored in 1958 by the Regional Office for Europe of the World Health Organization, are available for persons officially or professionally concerned in this field of study on request to the W.H.O. Regional Office for Europe, Copenhagen, Denmark.

CYTOGENETIC STUDIES IN ACUTE LEUKAEMIA

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Abnormalities of the chromosomes of leukaemic cells in human acute leukaemia have now been the subject of several reports (Ford *et al.*, 1958b; Baikie *et al.*, 1959; Ford, 1960; Sandberg *et al.*, 1960). It would appear that in about half the cases reported some abnormality has been found, including aberrations of chromosome number, morphology, and sometimes both of these. Among the reported cases no two appear to have had an identical abnormality. In this respect, and as regards their frequency of occurrence, the chromosome abnormalities in acute leukaemia may be contrasted with the apparently specific chromosome abnormality which may be found in most cases of chronic myeloid leukaemia in man (Nowell and Hungerford, 1960; Baikie *et al.*, 1960; Tough *et al.*, 1961). It has not yet been possible to correlate any of the clinical or haematological features of acute leukaemia with the varied chromosome abnormalities which have been found. If any such correlations exist it seems probable that they will emerge only after the publication of many more data than are at present available. For this reason we now publish our accumulated cytogenetic results in 22 cases of acute leukaemia in adults, together with the relevant haematological data.

Seven of the 22 patients had a history of significant exposure to ionizing radiation. All seven had, during the preceding 12 years, received radiotherapy for some condition other than leukaemia, involving the irradiation of a large volume of tissue. None of the other patients had any history of radiotherapy. Our knowledge of the occurrence of leukaemia in irradiated individuals indicates that after a single heavy exposure the possibility of leukaemia being diagnosed rises to a maximum between the third and eighth post-exposure years, but may not have returned to normal levels in the twelfth year (Medical Research Council, 1960). In our seven patients with a history of previous radiotherapy there is therefore a high probability that leukaemia was radiation-induced. Inspection of our results suggests that demonstrable chromosome abnormalities may be relatively more frequent among cases of acute leukaemia which may be radiation-induced. Similarly, demonstrable chromosome abnormalities may be relatively more frequent in cases with unusually low white-cell counts. These possible associations can be confirmed or refuted only by the publication of many more data than are now available. With the continued accumulation of results, other associations of possible aetiological or pathogenetic significance may emerge.

In our previous paper on chromosome studies in acute leukaemia we published detailed results in one case and summarized data for four others (Baikie *et al.*, 1959). The complete data for these four cases are now reported together with results in 17 other cases, all of which were

studied before December 1, 1960. The results of similar studies in five cases of acute leukaemia associated with mongolism and three instances of acute transformation of chronic myeloid leukaemia have recently been published (Tough *et al.*, 1961).

Methods and Technical Considerations

The chromosome studies on bone-marrow were carried out by the method of Ford *et al.* (1958b). Peripheral blood leucocytes were cultured by a modification of the technique of Moorhead *et al.* (1960). Initially the chromosomes were spread by squashing between a slide and coverslip, but as this was found to result in a high proportion of broken cells they have more recently been spread by air-drying. The technique for the culture of peripheral blood leucocytes has several important advantages over the method in which bone-marrow is used.

Firstly, the proportion of failures in blood cultures from patients with leukaemia is very much lower than the proportion of failures in bone-marrow cultures from similar patients. Thus in 40 attempts to culture leukaemic marrow there were 25 failures to obtain suitable dividing cells compared with 9 failures in 31 attempts at blood culture. In no case did bone-marrow yield a result where peripheral blood failed to do so.

Secondly, the peripheral blood technique gives chromosome preparations of a very much higher standard than those obtained from bone-marrow cultures. The appearances of the chromosomes are much better in that finer degrees of morphological abnormality may be recognized; and blood preparations generally yield more cells of a quality suitable for chromosome counting.

Lastly, the peripheral blood method has obvious advantages with regard to the ease of obtaining samples, and consequent suitability for serial observations. Nevertheless, in spite of the advantages of peripheral blood culture we feel that it is desirable, at least in acute leukaemia, to attempt chromosome studies on both blood and bone-marrow. This view is confirmed by some of the results we now present.

In spite of the improvement in the number of cells suitable for chromosome counting brought about by the introduction of the peripheral blood method, cultures of leukaemic material yield fewer cells which can be counted than do similar cultures from non-leukaemic subjects. In blood cultures from non-leukaemic subjects there is usually little difficulty in finding at least 50 cells suitable for counting and, if necessary, for analysis. Unfortunately, even this modest number of dividing cells is sometimes not available in preparations of leukaemic blood. This is particularly regrettable, since the determination of the chromosome count distribution of leukaemic material requires the counting of more rather than fewer cells. In fact, it is difficult to set any upper limit to the number of dividing cells it may be desirable to count for the satisfactory determination of the chromosome constitution of leukaemic material. In part this is due to the limitations of the current methods of culture, which are discussed later.

As a consequence of these limitations an abnormal cell line may be grossly under-represented in the final chromosome preparations. If this should occur, examination of a large number of cells may increase the chance of detecting an abnormal cell line such as that found in the blood cultures from Case 21. Even if the culture techniques provide preparations which are representative of the cell population *in vivo* it may be desirable to count a very large number of cells. For example, in Case 1 the gross deviation from normal of the chromosome count distribution made it desirable to count as many cells as possible for the characterization of the four, or possibly five, cell lines. It is unfortunate that in Case 20, with almost as great diversity of chromosome number, fewer cells could be counted.

Chromosome Count Distribution

At present we must accept the regrettable difference between the number of cells it may be possible to count and the ideal number for the determination of the chromosome count distribution in leukaemia. For the purposes of this report we have been obliged to accept the counting of 30 cells as a minimum number for the determination of chromosome count distribution. Three observations in Table II are based on fewer than this number of cells, but are nevertheless reported in detail because of our earlier brief report of these cases. Several preparations from the new cases failed to yield 30 cells for counting, but in no instance is the finding of an abnormality of chromosome count distribution based on fewer than that number of cells. It should be noted that in four cases (Nos. 8, 9, 20, and 22) fewer than 30 cells could be counted in marrow preparations, while simultaneous observations on peripheral blood yielded more than that number.

The criteria we have adopted for the assessment of the chromosome count distribution in leukaemic blood and bone-marrow depends on comparison with the count distribution in preparations from individuals of apparently normal karyotype. We have taken as normal values an average of 85% modal diploid cells for marrow preparations made by squashing (Court Brown *et al.*, 1960); 78% for blood-culture preparations made by squashing (Jacobs, unpublished observations); and 94% for blood preparations dried in air (Tough *et al.*, 1960). A count distribution is regarded as abnormal if on comparison of the observed and expected proportions of modal cells a marked deficit ($P<0.01$) of modal (46 chromosome) cells is found. Where the P values are greater than 0.01 the count distribution is regarded as being within the limits of normal. One inadequacy of these criteria lies in their failure to differentiate between the proportions of hypodiploid and hyperdiploid cells among the non-modal cells.

These stringent criteria have been adopted empirically and in spite of the fact that it may be argued that comparisons of the chromosome count distribution of blood and bone-marrow preparations from leukaemic and non-leukaemic individuals are of doubtful validity. Thus it might be said that the greater spread of chromosome count distribution in leukaemic material is due to a greater liability to artifacts consequent upon the increased fragility of the leukaemic cells in some cases of leukaemia. In any event the adoption of these criteria makes it probable that in our results the frequency of abnormality of chromosome count distribution in leukaemic preparations will be underestimated. The adoption of these criteria serves to emphasize the need for basing the assessment of chromosome count distribution, especially in leukaemic material, on as many cells as can reasonably be counted. On the other hand, their uncritical application might lead to a failure to recognize evidence of undoubted chromosome abnormality in some cases.

The assessment of a possible morphological abnormality in chromosome preparations raises fewer

problems. If the same abnormality can be seen in a proportion of the cells studied this is accepted as good reason for regarding the case as one showing undoubted chromosome abnormality. The possibility of these abnormalities having arisen in culture seems improbable, since no similar abnormalities have been found in several hundred cultures from non-leukaemic subjects. Thus it appears reasonable to accept these changes as being directly associated with the leukaemic state.

Almost nothing is known about the possible effects of the treatment of acute leukaemia on the chromosomes of either normal or leukaemic cells. It is known, however, that agents such as 6-mercaptopurine may produce chromosome abnormalities (Biesele, 1958). It is likely that any treatment which effectively suppresses an abnormal cell line may influence the results of chromosome studies by altering or masking a chromosome abnormality previously present. Our own observations on the effects of treatment on chromosome abnormalities in acute leukaemia will be the subject of a separate communication. At present we feel that when attempting to score the frequency of chromosome abnormalities in acute leukaemia it is undesirable to count as such any chromosome abnormalities found in

TABLE I.—*Haematological Data—Cases of Acute Leukaemia Without History of Previous Radiotherapy*

Case No.	Age	Date of Diagnosis	Peripheral Blood	Bone-marrow	Leukaemic Cell Differentiation	Treatment (Other than Blood Transfusion)	Date of Chromosome Study	Peripheral Blood	Bone-marrow
1*	56	3/9/58	Hb 4·6, Retic. 0·6, Pl. 78,000, WBC 1,700 (N. 35, Ly. 50, Leuk. 15)	Leukaemic cells predominate	Myelo-monocytic	None	3/9/58	As before	As before
2*	64	14/5/59	Hb 9·0, Retic. 4·4, Pl. 95,000, WBC 8,400 (N. 7, Ly. 27, Mon. 6, Bas. 1, Leuk. 59)	Leukaemic cells present	Myeloid	P 15/5/59–	14/5/59 3/8/59	,, ,, Hb 7·8, Retic. 17, Pl. 73,000, WBC 9,700 (N. 35, Ly. 10, Mon. 8, My. 15, Leuk. 32)	,, ,, Acute myeloid leukaemia
3*	41	24/11/58	Hb 5·0, WBC 154,000	Acute myeloid leukaemia	,,	P –/12/58– M 17/12/58 B_{12} 5/1/58 F 20/1/58	5/1/59 19/1/59 10/2/59	Hb 7·9, Retic. 9, Pl. 73,000, WBC 20,000 (N. 31, Ly. 30, Mon. 3, Leuk. 36) Hb 5·1, Retic. 2, Pl. 48,000, WBC 4,800 (N. 28, Ly. 38, Mon. 2, Leuk. 32) Hb 3·5, Retic. 6, Pl. 57,000, WBC, 13,900 (N. 2, Ly. 15, My. 1, Leuk. 82)	As before with megaloblastic erythropoiesis Remains megaloblastic Leukaemic appearance unchanged; now normoblastic
4*	48	24/4/59	Hb 12·0, WBC 1,600 (N. 14, Ly. 82, Eos. 2, Mon. 2)	Leukaemic cells predominate	None	P 8/5/59	8/5/59 26/5/59	Hb 9·0, WBC 1,000 (N. 2, Ly. 97, Mon. 1) Hb 9·5, WBC 2,200 (N. 12, Ly. 70, Leuk. 18)	As before ,, ,,
5*	70		See Table III						
6	57	17/9/59	Hb 9·2, Pl. 30,000, WBC 40,000 (N. 2, Ly. 16, Eos. 6, Leuk. 76)	Leukaemic blast cells predominate	None	None	17/9/59 2/11/59	As before Hb 6·8, Pl. 20,000, WBC 72,000 (N. 4, Ly. 11, My. 1, Leuk. 84)	As before
7	29	6/10/59	Hb 8·8, Retic. 0, Pl. 50,000, WBC 57,000 (Ly. 12, Mon. 9, Leuk. 79)	,, ,,	Monocytic	,,	6/10/59	As before	,, ,,
8	57	–/1/58	Hb 8·3, WBC 3,500 (N. 24, Ly. 64, Mon. 2, My. 2, Leuk. 8)	Bizarre erythroid hyperplasia	Erythroid	P –/2/58 F –/2/58 B_{12} –/2/58 all continued	28/1/60	Hb 8·1, WBC 10,800, (N. 21, Ly. 18, Mon. 1, My. 12, Leuk. 48)	Bizarre erythroid hyperplasia with leukaemic blast cells
9	63	1/4/60	Hb 9·0, Retic. 1·0, Pl. 70,000, WBC 30,200 (N. 5, Ly. 10, Leuk. 85)	Leukaemic cells predominate	None	None	1/4/60	As before	As before
10	47	26/5/60	Hb 10·6, Retic. 9, Pl. 10,000, WBC 51,000 (N. 10, Ly. 5, Eos. 5, Mon. 4, My. 8, MMy. 4, PMy. 4, Leuk. 60)	Leukaemic blast cells predominate	Myeloid	,,	26/5/60	,, ,,	—
11	55	–/5/60	Hb 6·0, Pl. 75,000, WBC 1,200 (N. 27, Ly. 73)	,, ,,	Lymphatic	,,	7/6/60	Hb 11·0, WBC 2,500 (N. 18, Ly. 66, Leuk. 16)	—
12	57	28/6/60	Hb 9·0, Pl. 60,000, WBC 129,000 (N. 7, Ly. 19, My. 1, Leuk. 73)	Leukaemic cells predominate	Myelo-monocytic	,,	28/6/60	As before	—
13	70	26/10/60	Hb 6·0, Pl. 46,000, WBC 52,000 (N. 6, Ly. 16, Leuk. 78)	Leukaemic blast cells predominate	Lymphatic	,,	26/10/60	,, ,,	—
14	61	11/11/60	Hb 7·5, Retic. 6, Pl. 85,000, WBC 148,000 (N. 36, Ly. 2, Mon. 8, My. 3, PMy. 8, Leuk. 43)	Acute myeloid leukaemia	Myeloid	,,	11/11/60	,, ,,	As before
15	39	9/8/60	Hb 5·1, Pl. 48,000, WBC 4,000 (N. 36, Ly. 39, My. 3, Leuk. 22)	Myelo-fibrosis	Myelo-monocytic	P –/10/60– –/11/60 A –/11/60 B_{12} –/11/60	24/11/60	Hb 7·8, Pl. 23,000, WBC 16,000 (N. 14, Ly. 15, Mon. 10, My. 5, Leuk. 56)	—
16	28	24/11/60	Hb 6·7, Pl. 40,000, WBC 25,300 (N. 32, Ly. 27, My. 5, Leuk. 36)	Acute myeloid leukaemia	Myeloid	None	24/11/60	As before	

* Cases 1–5 previously reported by Baikie *et al* (1959).

Hb = Haemoglobin (g./100 ml.). Retic. = Reticulocytes (%). Pl. = Platelets (per c.mm.). WBC = White blood cells (per c.mm.). N. = Neutrophil polymorphs (%). Ly. = Lymphocytes (%). Eos. = Eosinophil polymorphs (%). Bas. = Basophil polymorphs (%). Mon. = Monocytes (%). My. = Myelocytes (%). MMy. = Metamyelocytes (%). PMy. = Promyelocytes (%). Leuk. = Leukaemic cells (%). P = Adrenal cortical steroid. A = Corticotrophin. M = 6-Mercaptopurine. B_{12} = Vitamin B_{12}. F = Folic acid.

treated cases if there is any possibility of these having arisen as a consequence of treatment. Nor can the possibility be excluded in any treated case that an abnormality of chromosome count distribution or morphology, although originally present, may no longer be demonstrable.

The haematological methods used were those of Dacie (1956). In addition, buffy-coat preparations of defibrinated blood were examined, particularly in cases with low peripheral white-cell counts. Whenever possible bone-marrow was examined in both film and squash preparations. It is our belief that, on the whole, attempts at cell-type diagnosis in acute leukaemia are pursued much further than is justified by the reliability of the criteria for distinguishing the various cell types. Nevertheless, in these studies we have attempted to distinguish any possible differentiation of the leukaemic cells in the hope that some correlation of cell-type with chromosome changes might be discerned. The decision concerning cell-type differentiation of the leukaemic cells is based on appearances in preparations stained with May–Grünwald–Giemsa. Account is taken of any evidence of cell-type differentiation either in blood or in bone-marrow at any stage of the disease for which material may be available to us. The inherent observer error in such decisions is greater than is generally recognized (Witts, 1960). We have satisfied ourselves of the magnitude of this error by repeated examinations in which the source of the preparations was unknown to the observers.

Results

For cases without history of radiation exposure the relevant haematological data and the cytogenetic data are given in Tables I and II respectively; and for cases with a history of previous radiation in Tables III and IV respectively. The results of chromosome studies in Cases 1–5 have been reported previously (Baikie *et al.*, 1959); in detail for Case 1, and in summary for Cases 2–5. The full data for Cases 2–5 are reported here, and in two of these the observations have been reassessed in the light of our greater experience. The data for Case 5 now appear in Tables III and IV along with the data for the other cases with a history of radiation exposure.

It will be seen that in 11 patients some abnormality of chromosome constitution was found in the blood or bone-marrow. The abnormalities found in Cases 2, 5, and 8 are not scored as such, either because the observations fail to satisfy our requirements or because possible effects of treatment cannot be excluded. In Case 2 both the cultures yielded an inadequate number of cells suitable for counting. Furthermore, it is possible that in the less unsatisfactory preparations of August 3, 1959, the excess of non-modal cells might be attributable to the effects of treatment. This reservation must also apply to the finding of an excess of non-modal cells in the preparations from the bone-marrow cultures in Case 5 and the blood cultures in Case 8. On the other hand, we have accepted Case 17 as showing definite chromosome abnormality. In this case there was a gross excess of polyploid cells, among which multiples of the haploid number up to sixteenfold were present. In addition, the modal diploid number was shifted to 42, with counts suggesting the presence of at least three cell lines. It seems unlikely that treatment with 6-mercaptopurine for 72 hours could have produced these gross changes in the chromosome count distribution. On the other hand, it might appear not improbable that the excess of polyploid cells was due to the effects of treatment. This possibility is, however, rendered highly unlikely by our knowledge of the appearances of haematological preparations of the bone-marrow made before treatment and at the time the sample was taken for cytogenetic study. In both these bone-marrow smears there were many bizarre multinucleated red-cell

TABLE II.—*Cytogenetic Data—Cases of Acute Leukaemia Without History of Previous Radiotherapy*

Case No.	Date	Whether Treated	Material	Chromosome Counts													Remarks
				Total	<43	43	44	45	46	47	48	49	>49	Polyploid	Endo-redup.	No. of Cells with 46 Chromosomes Expected	P†	
1	3/9/58	Untreated	Marrow	184	2	—	3	2	24	45	75	27	6	—	—	156·4	<0·001	Fully reported by Baikie *et al.* (1959)
2	14/5/59	,,	,,	12	—	2	—	1	3	3	2	1	—	6	—	10·2	<0·001	No analysis possible*
	3/8/59	Treated	,,	24	—	2	—	2	12	8	—	—	—	2	—	20·4	<0·001	,, ,, ,,
3	5/1/59	,,	,,	64	—	1	3	2	55	3	—	—	—	2	—	54·4	—	No abnormality seen*
	19·1/59	,,	,,	54	1	—	1	3	48	1	—	—	—	3	—	45·9	—	,, ,, ,,
	10/2/59	,,	,,	61	1	—	1	2	55	1	—	1	—	1	—	51·9	—	,, ,, ,,
4	8/5/59	Untreated	,,	42	—	—	2	3	36	—	1	—	—	—	—	35·7	—	Constant abnormality, possibly due to translocation or duplication
	26/5/59	Treated	,,	7	—	1	—	—	6	—	—	—	—	—	—	5·9	—	
5	See Table IV																	
6	17/9/59	Untreated	Marrow	26	—	—	1	3	22	—	—	—	—	—	—	22·1	0·9 <P>0·95	No abnormality seen
	2/11/59	,,	,,	21	—	2	1	1	16	1	—	—	—	—	—	17·8	0·02<P>0·05	,, ,, ,,
7	6/10/59	,,	,,	67	—	—	2	2	41	18	3	1	—	—	—	56·9	<0·001	Excess hyperdiploid cells. In most cells analysed this is due to extra small metacentric chromosome
8	28/1/60	Treated	Blood	48	—	2	10	13	18	3	1	1	—	—	—	37·4	<0·001	Excess hypodiploid cells.
	28/1/60	,,	Marrow	26	4	2	2	2	16	—	—	—	—	—	—	22·1	<0·001	No consistent abnormality
9	1/4/60	Untreated	Blood	30	1	2	2	3	18	2	2	—	—	2	—	23·4	0·01<P>0·02	No analysis possible
	1/4/60	,,	Marrow	29	—	2	1	4	22	—	—	—	—	1	—	24·6	0·1 <P>0·2	,, ,, ,,
10	26/5/60	,,	Blood	30	—	—	1	1	28	—	—	—	—	—	—	23·4	—	No abnormality seen
11	7/6/60	,,	,,	33	—	1	1	2	29	—	—	—	—	—	—	25·7	—	,, ,, ,,
12	28/6/60	,,	,,	36	2	—	—	2	32	—	—	—	—	—	—	33·8	0·2<P>0·3	,, ,, ,,
	28/6/60	,,	Marrow	31	—	—	—	3	27	1	—	—	—	—	—	26·3	—	,, ,, ,,
13	26/10/60	,,	Blood	40	1	—	1	2	36	—	—	—	—	—	—	37·6	0·2<P>0·3	,, ,, ,,
14	11/11/60	,,	,,	50	—	—	—	—	48	2	—	—	—	—	—	47	—	,, ,, ,,
15	24/11/60	Treated	,,	30	—	—	—	2	28	—	—	—	—	—	—	28·2	0·8<P>0·9	,, ,, ,,
16	24/11/60	Untreated	,,	30	—	1	—	1	28	—	—	—	—	—	—	28·2	0·8<P>0·9	,, ,, ,,

* Amended from previous report (Baikie *et al.*, 1959).
† χ^2 test. Here and in Table IV the test has been used when the observed number of cells with 46 chromosomes is less than the expected number. Expected numbers: marrow, 85%; blood (squash preparations), 78%; blood (air-dried preparations), 94%.

precursors which may reasonably be equated with the polyploid cells found in the chromosome preparations. These cells were quite as numerous before treatment as at the time of the chromosome studies.

In five cases (Nos. 1, 7, 17, 19, and 20) the chromosome abnormalities included a definite deviation from normal in the chromosome count distribution in accordance with the criteria adopted. The findings in Case 1 suggested the presence of as many as four cell lines with chromosome numbers of 46–49. The normal modal number of 46 was unchanged in Case 7, but there was an excess of hyperdiploid cells with a chromosome count of 47. In contrast, the alteration of modal number was to hypodiploid values in the three previously irradiated patients whose alteration in chromosome count distribution satisfied our criteria (Cases 17, 19, and 20). It is of interest to note that the only other satisfactory demonstration of a hypodiploid chromosome number in leukaemia was also in a patient who developed acute leukaemia some time after radiotherapy. This other case, reported by Ford *et al.* (1958b), had received a total dose of 34 mc of radiophosphorus for polycythaemia vera.

Where an alteration in chromosome number occurs in leukaemia it may be impossible to decide that particular chromosomes are consistently missing, or present in excess of the normal complement. This difficulty may be due to the presence of several stemlines, as well as to true variation from cell to cell in respect of the additional or missing chromosomes. Furthermore, attempts to identify these additional or missing chromosomes may be complicated by the concomitant occurrence of morphological abnormalities and chromosome fragments, as in Cases 1, 19, and 20. In spite of these difficulties it may sometimes be possible to characterize additional chromosomes which are consistently present. For instance, in Case 7, those cells with 47 chromosomes which could be analysed appeared to have an additional small autosome, probably in the group 19–20 (Denver classification). Reference may also be made to our findings (Tough *et al.*, 1961) in a patient with chronic myeloid leukaemia in the phase of acute leukaemic transformation. In this case there were present two distinct cell lines, one with 46 and one with 49 chromosomes. The hyperdiploid line was found to have a constant karyotype; each countable cell carried the Ph^1 chromosome associated with chronic myeloid leukaemia; and the three additional chromosomes comprised a medium submetacentric, a small metacentric, and a small acrocentric chromosome.

Besides the five cases with definite alteration of chromosome count distribution two others (Cases 4 and 21) had morphological abnormalities. In Case 4 an unusually large acrocentric chromosome was seen, possibly the result of a translocation or a duplication. In Case 21, of 52 diploid cells in preparations from peripheral blood leucocytes 6 cells had an abnormal large acrocentric chromosome which was probably due to either a translocation or a pericentric inversion involving one of the chromosomes in the medium-size range (see Fig.). This abnormality was not demonstrable in a marrow preparation.

The results in Case 22 are of particular interest and serve to indicate one of the limitations of the criteria adopted for the assessment of chromosome abnormality. Satisfactory preparations from a blood culture showed a normal count distribution and no morphological abnormality. Only limited success was obtained in the

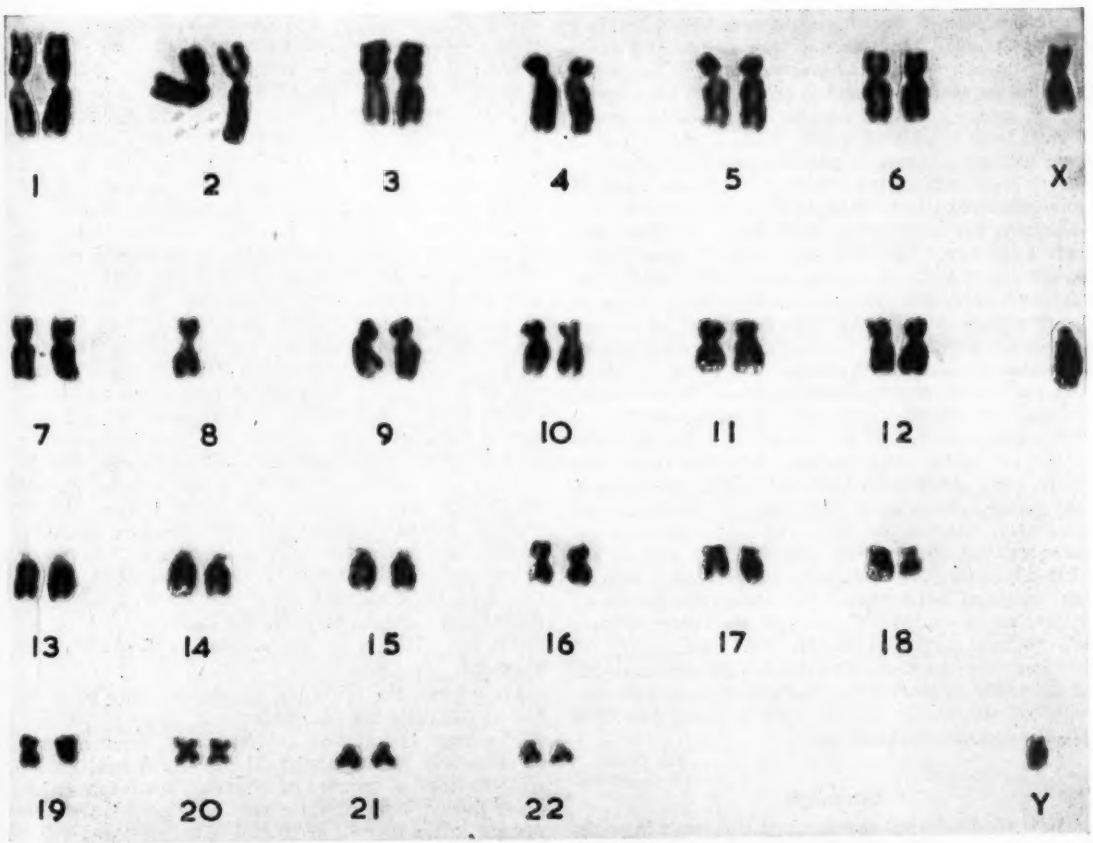
TABLE III.—*Haematological Data—Cases of Acute Leukaemia After Radiotherapy*

Case No.	Age	Primary Disease	When Irradiated	Date of Diagnosis of Leukaemia	Peripheral Blood*	Bone-marrow	Leukaemic Cell Differentiation	Treatment* for Leukaemia (Other than Blood Transfusion)	Date of Chromosome Study	Peripheral Blood*	Bone-marrow
5†	70	Polycythaemia vera	1945–57	1/9/58	Hb 6·5, Retic. 7, Pl. 20,000, WBC 400 (N. 18, Ly. 44, Mon. 4, Eos. 1, Leuk. 33)	Leukaemic blast cells and megaloblastic erythropoiesis	None	F 1/9/58 – 12/9/58 P 12/9/58	23/9/58	Hb 7·2, Retic. 5, Pl. 60,000, WBC 1,300 (N. 22, Ly. 53, Mon. 1, Eos. 2, Leuk. 22)	Leukaemic elements unaltered. Minimal megaloblastic change
17	44	Ankylosing spondylitis	1954–5	9/6/59	Hb 6·1, Pl. 65,000 WBC 3,400 (N. 34, Ly. 55, Mon. 1, Eos. 6, Leuk. 4)	Leukaemic blast cells and bizarre red-cell precursors	Erythroid	M 19/6/59	22/6/59	Hb 10·1, WBC 1,000	As before
18	59	,, ,,	1954, 1959	26/8/59	Hb 8·0, Pl. 62,000, WBC 18,800 (N. 60, Ly. 13, M. 12, Eos. 1, Bas. 1, Leuk. 13)	—	None	M 31/8/59 – 29/9/59 P 29/9/59 M 9/12/59 – 22/3/60 (intermittently)	8/12/59 22/3/60	Hb 12·1, Pl. 120,000, WBC 16,500 (N. 61, Ly. 23, Leuk. 16) Hb 11·4, WBC 56,700 (N. 49, Ly. 6, Leuk. 45)	Leukaemic blast cells present Unchanged
19	65	Polycythaemia vera	1953–9	6/5/60	Hb 8·6, Pl. 99,000, WBC 1,600 (N. 47, Ly. 29, Eos. 3, My. 1, Leuk. 20)	Leukaemic blast cells present	,,	None	6/5/60	As before	As before
20	56	Metropathia haemorrhagica	1954	9/6/60	Hb 7·1, WBC 750, (N. 12, Ly. 58, Leuk. 30)	Leukaemic cells present	,,	,,	9/6/60	,, ,,	,, ,,
21	75	Osteitis deformans	1954–8‡	27/10/60	Hb 10·1, Pl. 27,000, WBC 11,900 (N. 53, Ly. 9, Leuk. 38)	Myeloid preponderance with leukaemic blast cells	Myelomonocytic	,,	27/10/60	,, ,,	,, ,,
22	60	Menorrhagia	1949	11/11/60	Hb 11·7, Pl. 112,000, WBC 23,800 (N. 72, Ly. 11, Leuk. 17). Smear cells 150/200. WBC	Leukaemic blast cells present	Myeloid	,,	11/11/60	,, ,,	,, ,,

* Abbreviations as in Table I. † Previously reported by Baikie *et al.* (1959). ‡ Phenylbutazone, 1957–9.

TABLE IV.—*Cytogenetic Data—Cases of Acute Leukaemia After Radiotherapy*

Case No.	Date	Acute Leukaemia Treated or Untreated	Material	Chromosome Counts														No. of Cells with 46 Chromosomes Expected	P	Remarks
				Total	<40	40	41	42	43	44	45	46	47	48	>48	Polyploid	Endo-Redup.			
5	23/9/58	Treated	Marrow	30	—	1	—	2	1	1	5	19	1	—	—	—	—	25·5	<0·001	Excess hypodiploid cells. No analysis possible
17	22/6/59	,,	,,	35	2	2	6	13	6	2	1	3	—	—	—	106	—	29·7	<0·001	Great excess polyploid and hypodiploid cells
18	8/12/59	,,	,,	55	—	—	—	—	1	—	1	44	6	3	—	1	—	46·7	0·2<P >0·3	Possible excess hyperdiploid cells
	22/3/60	,,	Blood	21	—	—	—	—	1	2	3	13	2	—	—	—	9	16·4	0·05<P >0·1	Large number endoreduplications. Possible translocation
19	6/5/60	Untreated	,,	72	7	8	7	10	11	11	8	9	1	—	—	—	—	56·2	<0·001	58 cells showing structural abnormalities, including rings and fragments
20	9/6/60	,,	,,	45	—	—	4	9	18	4	2	6	2	—	—	—	—	35·1	<0·001	Fragments in 20 cells—all hypodiploid
	9/6/60	,,	Marrow	17	—	—	—	—	1	2	—	14	—	—	—	—	—	14·5	0·7<P >0·8	No analysis possible
21	27/10/60	,,	Blood	63	—	—	—	—	1	1	3	58	—	—	—	—	—	59·2	0·8<P >0·9	6 cells showing abnormally large acrocentric chromosome. No other abnormality seen
	27/10/60	,,	Marrow	41	—	—	—	—	—	—	—	41	—	—	—	—	—	34·9	—	No abnormality seen
22	11/11/60	,,	Blood	36	—	—	—	—	—	—	1	34	1	—	—	—	—	33·4	—	,, ,, ,,
	11/11/60	,,	Marrow	7	—	—	—	—	—	—	—	1	—	2	4	—	—	6·0	<0·001	3 cells—51 + fragment, all with 5 extra in medium-size range (7–12). 2 other cells had similar fragment



Cell with 46 chromosomes from Case 21 showing an abnormal large acrocentric chromosome.

attempt to culture marrow so that no more than seven cells were suitable for counting and analysis. Of these seven cells, three were found to have 51 chromosomes and a chromosome fragment, and a similar fragment was present in two other cells. Even in so small a number of cells the constancy of these findings must indicate the existence of at least one cell line of abnormal chromosome constitution. This result is accepted as evidence of a definite chromosome abnormality.

Examination of the chromosomes of skin cells was carried out as described by Harnden (1960) in Cases 1, 19, and 20. In all three cases the chromosome constitution of the skin cells was normal. This finding serves to associate the leukaemic state more certainly with the chromosome abnormalities demonstrated in bone-marrow cells in Case 1 and in peripheral blood leucocytes in Cases 19 and 20.

Chromosome preparations from all our cases of acute leukaemia have been examined for the presence of the abnormal chromosome associated with chronic myeloid leukaemia. In none of these 22 cases was the abnormality found, although it may occur where acute leukaemic transformation occurs in chronic myeloid leukaemia (Tough *et al.*, 1961).

The clinical and haematological features of all 22 cases have been reviewed in a search for features which may be correlated either with the frequency of occurrence of chromosome abnormality or with any particular type of chromosome abnormality. Where post-mortem examination was carried out these findings too have been considered. For these purposes 22 cases is a regrettably small series in a disease so variable in its manifestations. It may be pointed out that in no two cases has the same chromosome abnormality been found. By the strict criteria employed chromosome abnormalities were considered to have been found in 3 of 15 cases without a history of previous radiotherapy and in 5 of 7 cases with such a history. If less strict criteria were employed these would be 5 of 15 cases without a history of radiotherapy and 7 of 7 cases with such a history. Attention has already been drawn to the fact that all three cases with change of chromosome counts to hypodiploid values were in the previously irradiated group. There is no obvious association between the occurrence of chromosome abnormalities and the apparent leukaemic cell-type. All the cases were classified as undifferentiated, myeloid, lymphatic, monocytic, myelomonocytic, or erythroleukaemia. With the exception of the two cases in the lymphatic category, one or more cases with chromosome abnormality occurred in each of these cell-type classes. In contrast with this lack of correlation there may, however, be some association between the occurrence of chromosome abnormalities and a low white-cell count in the peripheral blood. Seven patients had counts of fewer than 5,000 white cells per c.mm. at the time of study. Of these, six are known to have died without the count having risen above 5,000; in the remaining case it did not exceed 10,000 before death. In this group of cases with notable and persistently low white-cell levels, only two cases (Nos. 5 and 11) failed to show undoubted abnormality.

Discussion

These results suggest that in acute leukaemia in adults there may be a relatively higher incidence of demonstrable chromosome abnormalities in cases with low white-cell levels and in patients with a history of significant radiation exposure. We do not intend to discuss the significance of these possible associations with reference to the problems of the aetiology and pathogenesis of acute leukaemia. It seems likely that the continued study of the chromosomes of leukaemic cells may provide information relevant to these fundamental questions. The present needs, however, are, firstly, for data such as we now report on many more cases of acute leukaemia; and, secondly, for some understanding of the relationship of the results obtained by current methods to the state of affairs *in vivo*. Such understanding may be obtainable either by different methods of chromosome study or by modifications of current methods based on knowledge of the metabolism and life-history of leukaemic cells.

The methods of short-term tissue culture at present in use in chromosome studies were developed for the optimal growth of normal peripheral blood leucocytes and bone-marrow cells. It is not surprising, therefore, that leukaemic material rarely grows as well as material from individuals who do not have leukaemia, and that sometimes it does not grow at all. The leukaemic cells in acute leukaemia probably differ from normal blood and bone-marrow cells in both metabolic requirements and in growth-potential. Furthermore, from one case of acute leukaemia to another the leukaemic cells may vary as widely in metabolic requirements and growth-potential as they do in numbers, morphology, and chromosome constitution. These differences, which presumably determine the success or failure of short-term cultures of leukaemic material, may not depend solely on the intrinsic properties of the individual leukaemic cells. Where normal cells are also present or where, as in Case 1, the leukaemic cell population is not homogeneous, interdependence and competition between the cell lines may be important.

At present there is little information available about which cells actually grow when normal blood and bone-marrow are cultured by the methods used in chromosome studies. Presumably in the case of normal bone-marrow the stem-cells of both the erythropoietic and granulopoietic lines proliferate. In cultures of normal peripheral blood leucocytes both direct observations (Nowell, 1960) and less direct evidence (Bond *et al.*, 1959) suggest that the cells which divide are those generally regarded as monocytes and large lymphocytes. In most leukaemic-marrow samples normal stem-cells must be present in large numbers and may compete successfully with the leukaemic cells in culture. In addition, there are other variable factors which may play a critical part when a tissue-culture method is used. These include differences between normal and leukaemic cells in regard to nutritional requirements and intermitotic times. Sampling errors, too, may be introduced either when the chromosome preparations are made from the cultured cells or, as seems less likely, when the original marrow sample is aspirated.

Presumably the operation of one or more of these factors accounts for our findings in Cases 8, 20, and 21, where there were chromosome abnormalities demonstrable in the peripheral blood cultures but no abnormalities in samples of bone-marrow taken at the same time. Some of these variable factors may also operate in the case of peripheral blood cultures, and it would be unwise to assume that in the peripheral blood

in acute leukaemia normal cells capable of division are entirely replaced by leukaemic cells. Thus in Case 22, in satisfactory preparations from peripheral blood, the cells were of normal chromosome constitution. In contrast, in the chromosome preparations from a much less successful marrow culture there was evidence of the presence of a cell line with undoubted chromosome abnormalities. In this case leukaemic cells were equally evident in smears of blood and bone-marrow, but those in the peripheral blood appeared to be extremely fragile, as indicated by the high proportion of smear cells in technically satisfactory blood films. Whatever interpretation may be preferred for the findings in this last case, it is obviously unwise to assume that in all cases of acute leukaemia the leukaemic cells in blood, bone-marrow, and other tissues are identical, at least as regards viability and growth potential.

Ford and Mole (1959) first pointed out that in cultures of marrow for chromosome studies normal cells may outgrow leukaemic cells and so fallaciously indicate a normal chromosome constitution where the leukaemic cells are in fact abnormal. The differences we have found between blood and bone-marrow appear to confirm the validity of their criticism. Sandberg *et al.* (1960) have tried to exclude the possibility of normal marrow cells outgrowing the leukaemic cells by the use of a method in which bone-marrow samples are fixed immediately after withdrawal. The results which may be obtained by this method have not as yet been compared with the results from cultures of the bone-marrow. The culture method provides technically superior preparations with many more dividing cells and thus makes possible the characterization of the chromosome complement of the stem-line or stem-lines. The results yielded by a more direct method such as that advocated by Sandberg and his co-workers could conceivably reflect a situation *in vivo* which cannot be re-created *in vitro*. The method used by Bottura and Ferrari (1960), in which a colchicine derivative is administered to the patient and chromosome preparations are made without preliminary culture of bone-marrow, may have the same merit.

In view of these admitted limitations of methods depending on short-term culture, it is obvious that, in individual cases of acute leukaemia, the finding of a normal chromosome constitution is less significant than the finding of an abnormality. It is interesting to note that Ford *et al.* (1958a) found chromosome abnormalities in a very high proportion of reticular neoplasms in the mouse, whether they were spontaneous or radiation-induced. In these studies the chromosome preparations were made directly from tumour tissue taken from animals previously given demecolcine (" colcemid "), so that culture was avoided. It may well be that with the methods at present available the most satisfactory chromosome studies in acute leukaemia could be achieved by combining a direct examination of bone-marrow with the culture of both bone-marrow and peripheral blood. In the future, with some knowledge of the nutritional requirements and life-span of leukaemic cells, it may be possible to adjust the conditions of culture from case to case, so that growth *in vitro* reflects more faithfully the position *in vivo*.

Summary

Chromosome studies have yielded satisfactory results in 22 out of 31 cases of acute leukaemia in adults. In eight cases results were obtained from bone-marrow, in seven cases from peripheral blood leucocytes, and in seven others from both tissues.

It is suggested that an attempt be made to establish criteria of chromosome abnormality applicable to leukaemic material. By the strict criteria adopted, chromosome abnormalities are thought to have been found in eight cases. Of seven patients with a history of significant exposure to radiation, five had undoubted chromosome abnormalities. In contrast, of 15 cases without such a history definite chromosome abnormalities were found in 3. Seven patients had white blood cell counts of fewer than 5,000 per c.mm. and chromosome abnormalities were found in five of them.

These findings suggest that the clinical and haematological features of cases of acute leukaemia should be considered and published with the results of chromosome studies. The possible association of chromosome abnormalities with these other features suggested by our results can only be confirmed or refuted by the accumulation of many more data than are at present available.

The limitations and possible disadvantages are discussed of methods of chromosome study dependent on short-term tissue culture.

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EFFECT OF D-THYROXINE ON SERUM CHOLESTEROL

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In the past few years much attention has been focused on the possibility of finding a thyroid "analogue" possessing one desired property of the natural hormone without the other, undesired, ones. In particular, repeated attempts have been made to find a substance which would depress the level of cholesterol in the serum without raising oxygen consumption or in any other way embarrassing the heart.

Starr and Liebhold-Schueck (1953) and Starr (1958) found that in human beings the metabolic activity of D-thyroxine (DT_4) is very slight compared with that of L-thyroxine (LT_4), the "D:L ratio" varying from 1:2 to 1:100 according to the method by which the activities were tested. They then thought that DT_4 had little effect upon the serum cholesterol in the doses used, though a response was shown by one patient treated with 10 mg. daily. However, Greene and Farran (1958) differed from Starr in finding that the level of cholesterol fell when the dose of DT_4 was raised enough, a minimum of 4 mg. a day and in some patients 10 mg. a day being needed. They found that the minimum dose needed to improve the clinical condition of hypothyroid patients was 4 mg. daily, but that some patients failed to improve when given 20 mg. daily. In no case was the B.M.R. raised by a dose smaller than 4 mg., and most patients needed 10 mg. or more. The D:L ratio in different patients varied between 1:10 and 1:50 or more.

At a symposium held in Chicago in December, 1959, much further information became available. Gesler *et al.* (1959) confirmed the previous work of Starr *et al.* and of Greene and Farran in showing that whereas DT_4 is only one-tenth as active calorigenically as LT_4, it is one-quarter as active in goitre inhibition, and therefore probably in T.S.H. suppression. Tapley *et al.* (1959) produced a possible explanation of the differing effects of the two isomers. They showed that three hours after their intravenous injection into rats there is twice as much DT_4 as LT_4 in the liver and kidney, whereas in the blood and other organs, including heart muscle, there is twice as much LT_4 as DT_4. One might therefore expect DT_4 to have a more profound effect on the liver (and therefore on cholesterol metabolism) and LT_4 a more profound effect upon the heart. That DT_4 (in equivalent "goitre-prevention doses") has a greater effect than LT_4 in diminishing liver cholesterol in the rat and rabbit was shown by Best and Duncan (1959) and by Kritchevsky and Langan (1959) respectively. Starr (1959) presented a series of cases of myxoedema with hypercholesterolaemia, diabetes with hypercholesterolaemia, idiopathic hypercholesterolaemia, and healthy controls treated with DT_4. In all hypercholesterolaemic cases the serum cholesterol levels fell, the doses used varying between 2 mg. and 26 mg. Usually 4 mg. was needed to lower a high cholesterol level. The effects were less consistent with a normal initial level. Changes in the B.M.R. and E.C.G. were rarely observed at a dose level below 10 mg. These results confirmed the findings of Greene and Farran. One patient with myxoedema, angina, and hypercholesterolaemia ceased to have angina when treated with 4 mg. of DT_4 daily, a finding consistent with that of Beaumont and Robertson (1939) and of the later workers who have reported relief of angina in myxoedema by treatment with thyroid. Hoobler, Caldwell, and Beierwalter (1959) obtained an average drop in the level of serum cholesterol to 21% below the initial level with a dose of 8 mg. The drop was sustained and there was no "escape" during long periods of observation. All 14 patients had hypercholesterolaemia without myxoedema; 8 had angina. None of these had an increase in angina, but in two the dose was lowered to 4 mg. because of thyrotoxic symptoms. Goldstein (1959) presented a series, which included cardiac patients. He concluded that at a dose level of 6 mg. daily DT_4 is a safe and innocuous drug. He was less impressed than other speakers by the decrease in serum cholesterol observed, but gave no figures. McCullagh and Sylvester (1959) treated 15 hypercholesterolaemic patients, all euthyroid, of whom nine had diabetes, three had previously had thyrotoxicosis, and one had arteriosclerosis. With doses of DT_4 which lay between 2 and 12 mg. there was a consistent return of the serum cholesterol to normal levels. One patient became hypermetabolic, a woman who had previously had Graves's disease. Jones (1959) made the important observation, not hitherto confirmed, that DT_4 produces an increase in prothrombin time in patients receiving anticoagulant therapy. He treated 14 patients with coronary disease with doses of 4 to 8 mg. daily. A 27% decrease in serum cholesterol was obtained and maintained for three to six months. Slight increases in metabolism and angina were observed when the dose was 8 mg., but the 6-mg. dose proved safe. Larson and Card (1959) did a "reversed double-blind test" using 4 mg. daily. In subjects with normal or slightly elevated levels of serum cholesterol there was a slight but consistent fall without any increase in metabolism.

At a symposium on derivatives and isomers of the thyroid hormones held in Philadelphia in February, 1960, further evidence was produced. Ruegamer (1960) stated that "diac" and DT_4 caused the greatest reduction in the liver cholesterol of rats of all the substances tested, with no effect on oxygen consumption or growth rate. Starr and Lepp (1960) described further clinical experiences. Oliver and Boyd (1960) called attention to the specific effect of thyroid analogues on cardiac muscle. They had seen angina increased under treatment with DT_4, but thought that this was the most promising of the substances tested. Starr (1960) administered DT_4 to three patients with myxoedema in a dose of 1 to 2 mg. daily. The serum cholesterol was lowered in three to four weeks from 500 to 300, 330 to 215, and 375 to 280 mg./100 ml. There was no significant change in the electrocardiograms or the basal metabolic rates. At the end of the study the latter were −36, −40, and −40% respectively.

Starr (1961), at the Fourth International Goitre Conference in London, presented a series of some 50 patients. He had found that, in untreated myxoedema, a dose of DT_4 as small as 1 or 2 mg. significantly lowered the serum cholesterol in 30 days without raising the metabolic rate or changing the E.C.G. In idiopathic and diabetic hypercholesterolaemia without hypothyroidism, the same results were achieved with doses of 2 to 8 mg. Patients suffering from angina had been maintained safely on 2 to 4 mg. The decrement was maintained during long periods of observation.

Boyd and Oliver (1960a), working with rats, showed that some iodothyronines cause a relatively greater depression of cholesterol levels with a relatively smaller increase in heart rate than others. They calculated a serum cholesterol/heart rate ratio and found this to be greatest for LT_3 and LT_4 and lowest for DT_4. They found (Boyd and Oliver, 1960b) that in human subjects the dose of most thyroxine "analogues" needed to keep low the cholesterol level was dangerously near the dose which produced angina, even when the B.M.R. was not increased. The exception was DT_4, which rarely led to angina in euthyroid men with coronary heart disease at a dosage of 7.5 mg. daily, though it reduced the level of cholesterol in the serum by an average of 25%. Cuthbertson *et al.* (1960) found that in rats fed on a diet which raised the serum cholesterol, three times as much DT_4 as LT_4 was required to affect the heart rate.

It would therefore seem that there is ample evidence that DT_4 lowers the level of serum cholesterol to normal in many cases; that the effective dose is from 2 to 10 mg.; that such doses rarely produce a significant rise in the B.M.R. and are in all other respects innocuous in the absence of ischaemic heart disease; and that in this condition DT_4 should be used with care but is probably safe when given in a dose of 4 mg. daily.

Before this information became available we had begun a trial of DT_4 in patients with hypercholesterolaemia, using the dosage suggested by previous work at New End Hospital (Greene and Farran, 1958).

TABLE I

Group	Diagnosis	No. of Patients Examined	No. with High Serum Cholesterol	No. Admitted to Series
I	Diabetes	214	23	11
II	Diabetes with atherosclerosis	69	11	3
III	Atherosclerosis	108	10	5
IV	Idiopathic hypercholesterolaemia	3	3	3
V	Idiopathic hypercholesterolaemia and myxoedema	1	1	1
VI	Disseminated lupus erythematosus	1	1	1
VII	Controls	6	0	6
		402	49	30

TABLE II.—*Effects of Treatment with DT_4 on Level of Serum Cholesterol*

Case No.	Cholesterol Levels Before Treatment (Averages in Parentheses)	Cholesterol Levels During Treatment (Time in Weeks from Beginning)													Maximum Depression from Average Level before Treatment
		2	4	6	8	10	12	14	16	18	20	22	24	26	
Group I															
1	298, 280 (289)			177		191		146		207		210		215	50
2	333, 358 (345)			203			217								41
3	295, 291, 267 (285)	240	214		205		187		182		222		255		36
4	294, 273, 332 (299)	255	318	297		259		238		260	290		294	318	27
5	400, 454, 413, 457, 411 (425)			358		400		288		305		225			47
6	325, 315, 317 (319)		250		282										22
7	324, 357, 321 (334)			203	241		282								40
8	308, 318, 304 (310)			280		278								249	20
9	375, 427 (401)					209		257		291					48
10	465, 443 (454)	325	238				372	333	304	296	312				35
11	351, 299, 306 (317)	389		371											38
			257		309										
Group II															
12	402, 362, 300 (355)			205	197	287			384		276		225	232	45
13	319, 327, 326 (324)		257		181				245		265		383	441	44
14	420, 370, 345 (378)		280		294		291		291		250		265		34
Group III															
15	240, 261, 400 (300)		272		246		256	214		252					29
16	331, 352, 351, 351 (346)	305	267	268						277		316	319	272	29
17	324, 283, 400, 295 (323)		232	218							301		319		23
18	405, 459 (432)	350					302				238				45
19	277, 293, 277 (282)		254		189	204		234	219	233		278		266	34
Group IV															
20	308, 308 (308)	262		251				189	205		225				39
21	299, 298 (298)	278		237		267		312		299		300		279	18
22	474, 471, 466 (472)		388	356	369	322	267		288	274		295		320	23
Group V															
23	315, 318 (316)	253	225	230			237	203	218		209	208	185	212	22
Group VI															
24	310, 309, 313 (310)	233		309		313		278	318			276		263	25
Group VII															
25	261, 235, 259 (252)		246		289		314		290		225	244	252	276	11
26	231, 302, 278 (270)		225		293										17
27	272, 296, 278 (282)		322		318										+12
28	285, 275, 285 (261)		239		221		271		286						16
29	306, 296, 254 (244)		226		298										3
30	254, 232, 258 (248)			257				223						294	10

Case 1: 10 mg. No side-effects. Levels normal after further three months. Case 2: 5 mg. No side-effects. Levels normal after further three months. Case 3: 10 mg. No side-effects. Levels normal after further three months. Case 4: 10 mg. Throbbing head. Dose reduced to 5 mg. after four weeks. No side-effects. Case 5: 5 mg. No side-effects. Case 6:—10 mg. Tachycardia. Experiment abandoned. Case 7:—10 mg. No side-effects. Case 8:—5 mg. No side-effects. Case 9:—10 mg. No side-effects. Case 10:—5 mg. Dose increased after 12 weeks to 10 mg. No side-effects. Case 11:—5 mg. No side-effects. Patient left district. Case 12:—5 mg. Despite coronary infarction dose increased after 16 weeks to 10 mg. No side-effects. Case 13:—10 mg. Despite absence of side-effects, dose reduced after 12 weeks to 5 mg. Case 14:—5 mg. Previously severe angina relieved. Case 15:—5 mg. No side-effects. Case 16:—5 mg. No side-effects. Case 17:—5 mg. After 20 weeks dose increased to 10 mg. No side-effects. An uncooperative patient who ceased to attend. Case 18:—5 mg. for 18 weeks. Dose then increased to 10 mg. for 4 weeks, then increased to 15 mg. No side-effects, but for safety's sake dose reduced to 10 mg. after 34 weeks. Levels normal (211 to 268, average 234) for a year since. Case 19:—10 mg. No side-effects, but dose reduced to 5 mg. after 4 weeks. Case 20:—5 mg. Dose increased to 10 mg. after 8 weeks. No side-effects. Case 21:—5 mg. No side-effects. Case 22:—Treatment initially with DT_3 reduced level to 350 in 10 weeks. Addition of 5 mg. and later 10 mg. of DT_4 produced no further effect. The effect of 15 mg. of DT_4 is shown. In the next 6 months the levels remained between 205 and 379, average 317. Case 23:—See text. Case 24:—10 mg. No side-effects. Cases 25–30:—See text.

Present Study

In order to determine the effect of DT_4 on the level of serum cholesterol, cholesterol determinations were made in the blood of patients in the groups shown in Table I. The maximum normal level of cholesterol in the serum was assumed to be 275 mg./100 ml. The discrepancy between the last two columns was due to practical, domestic, or geographical difficulties.

Methods.—In most cases periodic measurements of the B.M.R. and recordings of the E.C.G. were made before and during treatment. With few exceptions at least two, and usually three, determinations of the serum cholesterol were made before treatment. The initial "screening test" was performed in the hospital laboratory, but thereafter tests were performed at intervals of a fortnight in the Glaxo laboratories in order to obviate any differences in technique between the two hospitals in which the trial took place. Only the figures obtained in the Glaxo laboratories are recorded here. The method used was a modification of that of Zlatkis *et al.* (1953) after extraction by the technique of Abell *et al.* (1952). The doses of DT_4 are recorded in Table II. They varied between 5 and 15 mg. daily.

Results

Levels of Serum Cholesterol

The levels of serum cholesterol before and after treatment are shown in Table II. In group I (patients with uncomplicated diabetes mellitus) all patients but one showed a sustained drop in the level, the exception being a patient whose level dropped satisfactorily when he received 10 mg. but rose when, owing to "throbbing in the head," the dose was reduced to 5 mg. Of the patients in group II, one, who had had a coronary infarction, showed at first a satisfactory reduction on 5 mg. but "escaped"; 10 mg. produced sustained reduction without any deleterious effects on the heart. One in whom a good reduction was obtained with 10 mg. (without side-effects) could not be maintained by a dose of 5 mg. and relapsed. The third has been well maintained on 5 mg. for a year, his severe angina being completely relieved. In group III three patients showed a satisfactory reduction which has been maintained; one has shown a tendency to "escape" although the dose has been raised from 5 to 10 mg.; and one responded well to 10 mg. but has not maintained so low a level on 5 mg. In group IV one patient with a cholesterol level only slightly above normal failed to respond. Group V consisted of a single patient suffering from myxoedema. He was treated initially with triiodothyronine, which restored him to normal health. However, his serum cholesterol, which had averaged 458 before treatment, was reduced only to an average level of 350. When DT_4 (10 mg. daily) was added to his treatment no change in his B.M.R. or general health occurred, but the level of serum cholesterol sank to normal, and has remained since between 180 and 250 mg./100 ml. for a period of 14 months.

In group VI (one case of lupus erythematosus) the level of serum cholesterol fell from 313 to 233 mg. under treatment with DT_4 (5 mg. daily) in two months; when treatment was stopped it rose to an average of 311 mg. over a period of four months. Treatment with 10 mg. produced little effect, the range over the next five months being 263 to 318 (average 290 mg.).

In group VII were six diabetics who were not given DT_4. During the course of the experiment their levels of serum cholesterol, compared with the average before the experiment, varied greatly, the maximum reduction being of 16%—a warning to the optimists.

Effects on the Heart

In a previous experiment, abandoned and unpublished, we produced with "triac" a temporary angina in a healthy house-physician who was acting as a control. In consequence we were especially watchful for any deterioration in the cardiac condition of our eight atherosclerotic patients, all of whom had ischaemic heart disease. One patient in group I complained of "throbbing in the head" without tachycardia. Two patients in group I and one in group III developed tachycardia. In each case the dose was reduced to 5 mg., when the symptom disappeared, the cholesterol remaining normal. No patient developed angina *de novo* or experienced an exacerbation of pre-existent angina. One patient in group II, previously the victim of severe and frequent attacks, rapidly lost his pain, despite the fact that he had presented no evidence of myxoedema.

Effects of Metabolism

In no instance was there any change in the E.C.G., B.M.R., or pulse rate. The weights of the patients were not significantly affected.

Summary

D-Thyroxine (DT_4) in doses of 5 to 15 mg. daily is capable of reducing an abnormally high level of serum cholesterol, usually into the normal range. This effect is produced by doses too low to affect the E.C.G. or B.M.R. In ischaemic heart disease the drug should be used with caution, but no ill effects have been observed by us with doses not exceeding 5 mg. daily, and some patients in this category can tolerate larger doses. Some need a daily dose of 10 mg. to achieve the desired result. The drug is usually satisfactory in cases of atherosclerosis and diabetes, but in idiopathic hypercholesterolaemia the number of patients treated is too small for conclusions to be drawn.

The question of whether any benefit accrues to the patient when the level of serum cholesterol is reduced to a normal level remains still to be answered.

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LONG-CONTINUED INHIBITION OF GASTRIC SECRETION BY POLDINE METHOSULPHATE IN PATIENTS WITH PEPTIC ULCER

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Antacids are widely used to control pain and promote healing in patients with peptic ulcer. Although antacids, provided they are taken often enough and in large quantities (Clark and Hunt, 1958), are unquestionably effective in maintaining a lowered acidity in the gastric contents during the day, they have no influence on the acidity of the gastric contents during sleep. Instead of neutralizing the acid after it is secreted, it would seem better to try to inhibit the secretion of acid continuously even when the patient is in remission. This paper is concerned with treatment of patients with peptic ulcer along these lines, using an anticholinergic substance, poldine methosulphate (" nacton "), which reduces by about one-half the gastric secretion of acid without producing noticeable side-effects.

Present Investigation

In-patients of a previous trial (Douthwaite and Hunt, 1958) and several new patients have been followed as out-patients for periods up to three years. All those studied were admitted to the wards under the care of the consultant physicians because a full course of medical treatment under the best conditions was necessary. With the permission of the clinicians concerned, the trial was discussed with the patients. All except one of those approached accepted the offer.

Relevant facts about the patients, who are all men, are summarized in Table I. The mean duration of their dyspepsia was 10 years, two patients had gastric ulcers and 14 had duodenal ulcers. For the most part the diagnosis rested on the clinical history and radiology. In two there had been a perforation and in two others melaena. Ten had lost more than five weeks from work.

Procedure.—The patients were studied in the wards with test meals first while on dummy tablets and then on poldine, the dose being slowly increased until the patients noted some side-effect attributable to anticholinergic action. The amount was then reduced by 1 mg., or occasionally 2 mg., for each of the four daily doses, until the side-effect was abolished. During their treatment as in-patients they received in addition diets and antacids in accordance with the custom of the clinicians concerned. On their discharge, arrangements were made for the patients to attend for a test meal once a month, having taken their poldine on rising. On these occasions they were encouraged to report even mild dyspeptic symptoms that had occurred during the previous month. Their food was entirely of their own choosing, and antacids in the form of " prodexin " were made freely available.

Test-meal Method.—The method used for assessing the effect of poldine on gastric secretion has been described by Douthwaite and Hunt (1958). In essence it allows the total amounts of acid and chloride secreted in response to a test meal in 30 minutes to be measured by adding the amounts of acid and chloride recovered from the stomach to the amounts calculated to have passed into the duodenum. The amounts of acid and chloride can then be converted into the volumes of the acid component and the volumes of bicarbonate-containing secretion formed by the stomach (Hunt, 1954). The test-meal consists of 750 ml. of a solution containing 50 g. of glucose per litre, which is given down a tube into the stomach after an initial washout.

Dose of Poldine and its Side-effects

The dose of poldine was adjusted for each patient so that he did not notice any side-effects, such as dryness of the mouth, slowness in passing urine, or blurring of vision. As experience accumulated it became apparent that there were sometimes other side-effects that might indicate overdosage.

One patient took a double dose of poldine by accident and complained of severe headache, which ended very abruptly. One patient (Case 5, Fig. 2) noted eructations in the afternoon with an unpleasant odour after eating eggs. The symptom disappeared on reducing the dose. One patient reported reduced potency in the sexual act without loss of libido. As he was able to judge which of two lots of tablets were dummy, using his potency as an index, it was presumably a genuine side-effect. The other patients have not had the same experience. Potency was restored by a small reduction of the evening dose. One man, aged 35, noted slight breathlessness as a possible side-effect. No one noted constipation as a side-effect, although physicians using larger doses of poldine have reported it in their patients.

Tachycardia and extrasystoles, both unnoticed by the patients, have been found. It has been taken as a general rule, possibly overcautiously, that the heart rate should not be allowed to exceed 90 a minute at about two to three hours after the last dose of the drug. This has been made the limiting factor for 3 patients out of 16. In two patients extrasystoles were found occasionally, these were abolished by reducing the dose of the drug.

In one patient (Case 8), who had an excessive hypersecretion before treatment, it appeared that in spite of dryness of the mouth, the gastric effect of the drug was sometimes inadequate to relieve his symptoms. He was given his treatment in five divided doses instead of four, and in this way was able to take more poldine with fewer side-effects and with concurrent more effective control of his dyspepsia. Presumably, by giving the poldine more frequently the concentration at the

sites of action was kept more stable. Early experience with poldine given eight-hourly indicated that six-hourly doses were desirable even though the drug was clearly inhibiting gastric secretion eight to ten hours after the last dose. With the single exception of Case 8, it has never appeared that reducing the dose to eliminate side-effects has simultaneously caused an increase in gastric secretion of acid. Thus from experience we conclude that side-effects indicate that the dose is larger than need be. From time to time the dose for each patient has been raised, but in most instances it has been necessary to reduce it again because of side-effects. Thus, apart from the increase in tolerance noted during the first three weeks of treatment, there has been no significant change during the three years of this study.

Results

It may be seen from Table I that 14 out of the 16 patients taking a mean dose of 30 mg. of poldine a day have been followed for three years or more at the time of writing (February, 1961). The follow-up is complete except for three patients not referred to in Table I. The diagnosis for one of them was proved to be wrong. One patient followed the treatment for three months only, although dropping in afterwards from time to time to say that he was still having bouts of dyspepsia. Eventually he was admitted into the surgical wards for gastrectomy, but at the operation the stomach and duodenum were apparently normal, so that nothing further was done. When last seen he was well. One other patient was not followed because he did not take the drug regularly.

Column 8 of Table I shows a fraction, the numerator being the number of occasions on which the patient reported that since his previous visit there had been no dyspepsia, nausea, or any other symptom associated with his peptic ulcer. The denominator is the total number of visits. There were reports of complete freedom from dyspepsia in 83% of the 429 months at risk. This part of the study was started after the patients had been taking a placebo for one or two months in order that toxicity could be sought. For this purpose comparisons were made between data for full blood counts, urine analyses, serum bilirubin, and blood urea after the patients had been taking poldine for periods of up to 12 months, and after they had been on dummy tablets for one to two months. A careful study of these data revealed no evidence of toxicity.

All the patients were convinced that they were much better while taking poldine than they were before. As objective evidence for clinical improvement, it may be seen from Table I that since the beginning of treatment the total loss of time from work with dyspepsia had been two days in Case 5, four days in Case 12, and 14 days in Case 13. This loss of working-time should be compared with that noted in the previous column: the mean loss of work before treatment was four weeks per annum per patient. The patients were advised to take antacids if they had even mild dyspepsia. On each visit they were offered a supply of prodexin, but the majority, Cases 3, 8, and 16 excepted, said that the supply they had at home remained untouched.

Fig. 1 contains the data for Case 14 on the gastric secretion of acid in response to test meals at about monthly intervals for the three years of treatment. This record is given because it shows the increase in gastric secretion of acid two days after the patient's father had died tragically. Shay, Sun, Dlin, and Weiss (1958) found that an anticholinergic drug blocked the response to stress. As the response of our patients to a comparable tragedy without poldine methosulphate is not known, our data are not relevant to this point. Fig. 2 shows similar data for Case 5. The pain in this patient seems to be related to his domestic circumstances and he shows rather regular changes of gastric secretion with time. When he began to complain of eructations it seemed possible that poldine was reducing the efficiency of the cardia, as does atropine (Bettarello, Tuttle, and Grossman, 1960). When the dose was reduced there was no corresponding increase in gastric secretion, but the eructations did not recur. So far as it goes, this sequence of events is consistent with the possibility that a suitable dose of poldine could reduce gastric secretion of acid without increasing oesophageal reflux in patients subject to it.

TABLE I.—*Clinical Data on Patients Taking Poldine*

Case No.	Age	Beginning of Dyspepsia	Duration of Longest Remissions before Treatment with Poldine	Diagnosis	Beginning of Treatment with Poldine	Dose of Poldine mg./day	No. of Months Free of Dyspepsia/No. of Months at Risk	Patient's Comments	Time Off Work before Treatment with Poldine	Time Off Work after Treatment with Poldine
1	31	1957	1–8 weeks	D.D.	5/59	40	12/13 I	Completely unaware of digestive organs	20 weeks	Nil
2	39	1956	1 year	G.U.	9/57	28	22/27 I	One 14-day period with pain, 1960	3 ,,	,,
3	47	1945	12 weeks	D.D.	12/57	24	22/32	Almost always free of pain. No trouble in cold weather	2–4 weeks/year	,,
4	65	1956	3 days	D.D.	4/57	28	30/31	Free of trouble	9 weeks	,,
5	31	1950	5 weeks	D.D.	9/57	32	22/32	Occasional mild pains only	At least 20 weeks	2 days
6	66	1955	Continuous	M. D.D.	9/57	16	26/29 I	Free of trouble	3 weeks	Nil
7	28	1955	4 days	Pyloric ulcer	5/59	38	10/12 I	No pain or sickness	Not assessable, because a casual worker	,,
8	48	1954	3 years	P.D.U.	11/57	50	21/33	Occasional mild distress	210 days since 1954	,,
9	48	1952	4 weeks	M. D.U.	7/57	24	29/30 I	No pain even on night shift	3 weeks	,,
10	29	1953	2 ,,	D.D.	6/57	36	21/24 I	Almost always free of pain	5 ,,	,,
11	35	1953	3 ,,	D.D.	2/58	24	19/23 I	Eats and drinks without fear. Never so well before	3 weeks/year	,,
12	26	1951	3 weeks after perforation, then 18 months	P.D.U.	8/57	26	19/24	Some pain before marriage	100 days in hospital 1951–7	4 days
13	31	1946	12 weeks	D.D.	2/58	44	23/29	Pain on occasional days	100 days since 1956	14 ,,
14	32	1945	12 ,,	D.D.	8/57	44	24/28	Usually free of pain, occasional 2-day upsets	5 weeks	Nil
15	54	1926	2 years	G.U.	6/57	12	26/32	Usually free of pain	6–8 weeks/year since 1943	,,
16	37	1953	12 weeks	D.D.	8/57	28	23/30	Occasional mild pain	10 weeks	,,

D.D.=deformed duodenum. G.U.=Gastric ulcer. M.=Melaena. P.D.U.=Perforated duodenal ulcer. I=Recent radiological evidence of less deformity of duodenum.

Relation Between Radiological Studies and Clinical Response

Recently one of us assessed radiologically the change in the degree of deformity of the duodenal cap in the 14 patients with duodenal ulcer.

In six patients comparison of serial views taken before this trial was started showed that the degree of deformity of the duodenal cap had decreased. Presumably this was due to the fact that at least part of the initial deformity was caused by spasm associated with ulceration, and that this spasm was no longer present. It was therefore assumed that the above represented radiological evidence of an improvement. In eight cases

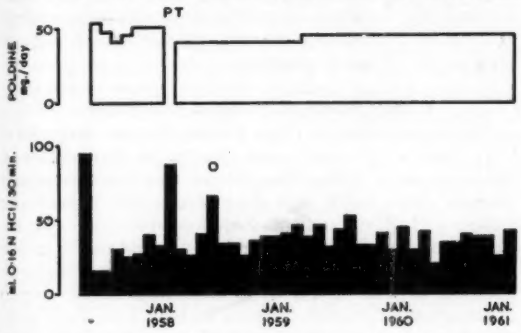

FIG. 1.—Case 14. Data on symptoms and gastric secretory responses to test meals at monthly intervals on poldine. P=Pain. O=Father died tragically. T=Tachycardia.

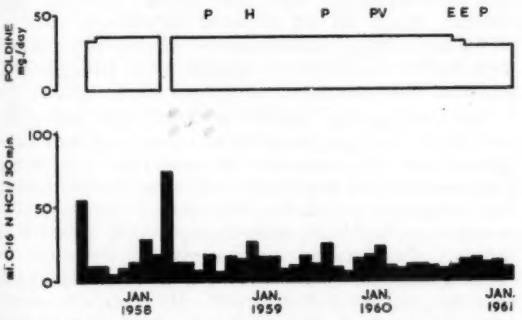

FIG. 2.—Case 5. Data on symptoms and gastric secretory responses to test meals at monthly intervals on poldine. E=Eructations. P=Pain. H=Heartburn. V=Vomiting.

there was no noticeable change, and it was therefore not considered possible to assess the true condition of the duodenal cap. If the initial deformity was in fact due to scarring, although the patient's present condition might suggest an improvement, the radiological findings were bound to remain unchanged. If ulceration and spasm played some part in the original deformity, the fact that this had persisted might suggest that spasm and/or ulceration were still present. There was no evidence of a crater or residual deformity in the two patients with a history of gastric ulceration.

Those patients in whom the deformity became less are marked in column 8 of Table I with the symbol I. It was found that those with radiological improvement in their duodenal caps had significantly more months free of dyspepsia—89% as compared with 77%—than those with duodenal caps unchanged. This difference is statistically significant at the one-in-fifty level. It may also be seen from Table I, column 9, that the patient's assessment of his response was particularly favourable in these six patients. There was, however, no evidence that poldine was more effective in reducing the secretion of acid in these patients than in the others.

Studies of Gastric Secretion and Emptying

The method of studying gastric secretion allows the amount of two hypothetical components of gastric secretion—the parietal and non-parietal—to be assessed separately. The parietal component is regarded as containing 160 mN hydrochloric acid, which is the concentration at which it is supposed to be secreted by the parietal cells. The non-parietal component, formed by the mucus-secreting cells of the whole gastric mucosa, is thought to contain 45 mN bicarbonate. In effect this means that 3.6—160/45—parts of non-parietal component neutralize 1 part of parietal component. The result is that failure to recover acid from the stomach is assessed by this method as due to the secretion of some parietal component balanced by 3.6 times as much non-parietal component.

This report deals with 351 studies of gastric function during out-patient treatment and 58 control studies while the patients were taking dummy tablets as in-patients and out-patients.

It may be seen from Table II, columns 4 and 5, that there was about half as much secretion of the acid parietal component when the patients were taking poldine as when they were taking dummy tablets. It seemed possible that a selected group of the patients — for example, those with marked hypersecretion—would be specially sensitive to the action of poldine, so that their secretion would be more inhibited than that of patients with lower secretions of acid. To test this view the mean amount of parietal component secreted while a patient was receiving dummy tablets was plotted against the mean amount secreted while he was taking poldine tablets as an out-patient. The data for the 16 patients are shown in Fig. 3. It may be seen that the data fit reasonably well on to a straight line, so that there is no evidence that the drug is more effective in inhibiting secretion in hypersecreters than it is in those with lower rates of secretion. It may also be seen that the slope of the line is such that for each 2 ml. of secretion with dummy tablets there is 1 ml. while the patients are taking poldine.

On the other hand, the secretion of non-parietal component was reduced by only 22%, so that the acidity of the mixed parietal and non-parietal components, the gastric juice, fell from a mean of 100 mN without poldine to 74 mN with poldine.

TABLE II.—*Effect of Poldine on Gastric Secretion and Emptying with Test Meals of 30 Minutes' Duration*

Case No.	Volume of Gastric Contents (ml.)		Volume of 0·16 N HCl Secreted (ml.)		Volume of 0·045 HCO_3^- Secreted (ml.)		Concentration of Acid in Gastric Juice (mN)	
	D.	P.	D.	P.	D.	P.	D.	P.
1	410	304	83	29	53	32	80	52
2	290	355	50	19	46	41	61	20
3	540	502	97	58	40	30	100	90
4	270	170	103	57	19	17	128	112
5	545	400	69	15	32	24	95	33
6	440	445	67	42	32	23	94	87
7	385	446	47	16	27	24	85	37
8	452	510	155	83	50	40	110	93
9	354	374	75	38	24	17	110	96
10	480	500	32	22	20	20	81	62
11	433	396	88	39	27	16	112	100
12	233	395	93	46	27	27	114	84
13	328	383	94	36	18	17	127	94
14	340	310	91	35	32	26	107	72
15	283	272	55	20	30	23	88	50
16	372	382	103	66	33	33	110	92
Means	384	387	81	39	32	25	100	73

D.=Dummy. P.=Poldine.

The mean volume of the gastric contents remaining in the stomach after 30 minutes, which may be regarded as an index of gastric emptying, was unchanged by the treatment with poldine.

Discussion

The main object of this trial was to determine whether poldine would be effective in reducing the gastric secretion of acid in patients with peptic ulcer going about their ordinary life. To judge from our data, poldine reduces gastric secretion by about one-half two to three hours after the drug is taken. In an earlier study of patients in hospital (Douthwaite and Hunt, 1958) it was found that the gastric secretion of acid was 45% of the control two to three hours after the dose and 60% of control 8 to 9 hours after the dose. From this finding and our current data, it is reasonable to assume that with four doses a day there will be a reduction of the secretion of acid at all times. This expectation is confirmed by the results of a few tests in our out-patients when they did not take their morning dose.

The data quoted above refer only to the reduction in the amount of parietal secretion formed in response to a glucose solution which probably stimulates by distension (Hunt and Macdonald, 1952). However, in further studies in conjunction with Drs. M. I. Grossman and R. D. Mitchell it has been found that there is with poldine a large reduction of the acidity of the gastric contents after an appetizing breakfast. In addition, Dr. Leonard Jones, in a communication to the Gastro-enterological Society in 1960, reported that poldine caused a significant reduction of acidity in the gastric contents with meals of milk which were found by Douthwaite and Hunt (1950) to be powerful stimuli to gastric secretion in patients with duodenal ulcer. Finally, Seidelin (1961) has reported a reduction of about 50% in basal secretion and in the response to maximal stimulation with histamine in patients with duodenal ulcer receiving doses of poldine adjusted to give no side-effects. It is usually a fair generalization to say that any means which reduces the response to "maximal" doses of histamine will reduce the response to all stimuli. Thus Seidelin's report probably applies to secretion in response to food.

When a drug reduces the amount of acid parietal component secreted in response to a standard stimulus, a corresponding or greater reduction in the secretion of the alkaline non-parietal component may leave the concentration of acid in the mixed secretions—that is, the gastric juice—unchanged or even increased. In our studies, however, the secretion of the non-parietal component fell by a smaller proportion than the secretion of parietal component, so that the mean concentration of acid in the gastric juice fell from 100 mN to 74 mN.

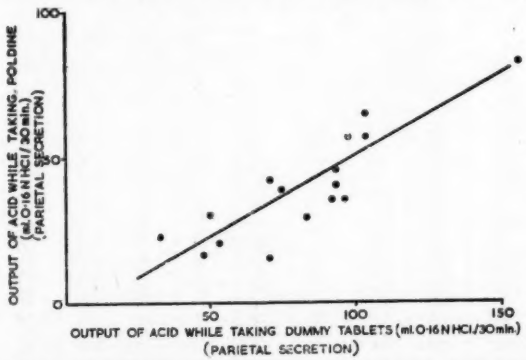

FIG. 3.—Comparison of gastric secretory responses to test meals by patients with and without poldine. Data based on 58 tests with dummy tablets and 351 tests with active tablets.

Poldine had no action on gastric emptying in our patients. However, this is no disadvantage, since it has not been possible to show that gastric emptying in patients with duodenal ulcer is different from that of healthy young persons (Hunt, 1957a, 1957b). The specificity of the action of poldine on gastric secretion is possibly an advantage, since slow emptying may increase the duration of gastric distension and contact of food with the antral mucosa, both of which may be expected to stimulate secretion.

Clinical Results of Treatment with Poldine

The clinical data in Table I show that our 16 patients lost a total of 20 days' work during the three years of the trial, while before they began treatment the mean absence from work was four weeks per patient per annum. Had our patients not improved clinically, we could have concluded that poldine was not useful in our context. The great reduction of loss of time from work does not logically allow us to conclude that the degree of reduction of acidity achieved with poldine is clinically useful. A full course of medical treatment in hospital followed by regular visits to an interested doctor, the continuous taking of tablets in an atmosphere of hope, and the knowledge that their gastric secretion was reduced, might all be expected to play a part in producing clinical improvement. However, some of these factors must always operate when patients with duodenal ulcer are given continuous medication.

Pharmacologically, poldine methosulphate was effective in reducing gastric secretion of acid without side-effects in out-patients for periods up to three years, since there was a return to control levels when dummy tablets were given for a month. Our clinical data are also consistent with poldine being therapeutically effective in reducing the duration and severity of dyspepsia in patients with duodenal ulcer and in greatly reducing the time they are away from work. However, the causal relationship between the reduction in gastric secretion of acid in patients with duodenal ulcer and the improvement in their clinical course remains open.

Clinical Use of Poldine

The following points are important in the effective use of poldine:

1. The dose should be given on rising, at 12 noon, at 6 p.m., and on retiring.

2. The dose should be built up gradually from 2 mg. per dose, and the total daily amount increased by 4 mg./day at four-day intervals.

3. Once definite side-effects are noted the dose should be reduced by 1 mg. or sometimes 2 mg. until they are no longer noted.

4. From our experience, a dose producing severe side-effects is not usually more effective in reducing gastric secretion of acid than a dose producing no side-effects.

5. Because poldine is pharmacologically active the dose should be carefully adjusted for each patient, and he should be seen at least at monthly intervals until it is clear that there is no undue tachycardia. Once the dose has been decided by trial, tolerance does not develop.

6. Should it be necessary to stop giving poldine for some days—for example, during pyrexia—it is important to build up the dose again gradually to avoid the possibility of marked side-effects on restarting with a full dose. In every instance the omission of one dose has abolished all side-effects.

7. The full effect of the drug on gastric secretion and on symptoms may take up to 21 days to appear. In the meantime the dyspepsia can be treated with antacids.

8. It is important to realize that poldine does not completely abolish the dyspepsia in all patients. In our experience it greatly reduces the number of occasions on which there is pain and it reduces the severity of the pain. However, overwork—for example, decorating a flat in the evening, long hours of overtime in a bank, or concreting a garden path—has raised the gastric secretion in response to test meals on the following day, and sometimes apparently caused dyspepsia in spite of continuous treatment with poldine. It is remarkable how slow even intelligent patients are in relating their symptoms to overwork. They have in our experience always responded to antacids.

Summary

Fourteen men with duodenal ulcers and two with gastric ulcers have been studied for a mean period of three years.

During this time they have been under treatment with four daily doses of poldine methosulphate ("nacton") just small enough to produce no side-effects. No tolerance developed.

The secretion of acid, as assessed at monthly intervals with test meals, was reduced by one-half by the drug as compared with the secretion with dummy tablets. There was no change in gastric emptying.

The patients were free of dyspepsia for four-fifths of the months of treatment. As compared with an average absence from work of four weeks per patient per annum before treatment, the mean loss of time from work was half a day per annum during the three years of the study. During this period the deformity of the duodenum was reduced in 6 out of 14 patients with duodenal ulcer. These six had less dyspepsia than the others.

The trial has established that poldine can reduce the secretion of acid by about one-half in out-patients with peptic ulcer. Simultaneously, dyspepsia and loss of time from work were much reduced. The trial does not establish that the reduction of secretion of acid and the clinical improvement are cause and effect, although the results are consistent with this view.

We thank Drs. C. G. Baker, E. R. Boland, R. Kauntze, K. S. Maclean, and W. N. Mann for their co-operation in our studies of patients under their care. We are indebted to Beecham Research Laboratories Ltd. for generous supplies of nacton (poldine methosulphate) and prodexin (aluminium glycinate and magnesium carbonate).

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ORAL TREATMENT OF PERNICIOUS ANAEMIA WITH VITAMIN-B_{12}–PEPTIDE

BY

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The earliest treatment of pernicious anaemia was the inclusion of large quantities of liver or kidney in the patient's diet (Minot and Murphy, 1926; McCann, 1929). Oral administration of extracts and digests from these organs followed (Porter *et al.*, 1929; Davidson, 1932; Davis *et al.*, 1943), and remissions were also obtained by giving desiccated hog's stomach (Sturgis and Isaacs, 1929; Sharp, 1929; Wilkinson, 1930, 1949). All of these preparations, though effective, were unpleasant and could not be sterilized. They were therefore largely replaced by parenteral injections of liver extract and later of cyanocobalamin (vitamin B_{12}). Small amounts of the latter have been combined with extracts of desiccated hog's duodenal and pyloric mucosa to provide palatable oral substitutes, but in spite of good initial therapeutic results most long-term maintenance studies have shown high relapse rates (Adams, 1957; Bastrup-Madsen, 1957; Killander, 1957; Kristensen *et al.*, 1957; Lowenstein *et al.*, 1957; Schwartz *et al.*, 1957; Berlin *et al.*, 1958; Pedersen and Ebbesen, 1958; Stokes and Pitney, 1958; Blackburn *et al.*, 1959; Ellenbogen *et al.*, 1960).

Orally administered crystalline vitamin B_{12} alone, either in single massive doses of 3,000–9,000 μg. or in smaller daily doses of 5–50 μg., have been shown to produce rises in haemoglobin concentration, red-cell count, and packed cell volume when given to cases of pernicious anaemia in relapse (Chalmers and Hall, 1954; Estren and Wassermann, 1956). Clinical and haematological remissions have been maintained by giving orally 1,000–3,000 μg. every one to four weeks (Conley and Krevans, 1955; Reisner *et al.*, 1955; Unglaub and Goldsmith, 1955) or 50–500 μg. each day (Chalmers and Shinton, 1958; Brody *et al.*, 1959; McIntyre *et al.*, 1960). However, with doses less than 150 μg. daily or 1,000 μg. weekly the serum vitamin B_{12} concentration remained abnormally low in some patients.

It has more recently been claimed that patients with pernicious anaemia can be adequately maintained on oral daily doses of 10 μg. of vitamin B_{12} when the latter is combined as a peptide complex derived from fermentation (Heathcote and Mooney, 1958). This has since been disputed by Varadi and Elwis (1960). Having made a study of orally administered crystalline vitamin B_{12} alone in cases of pernicious anaemia (Chalmers and Shinton, 1958), the opportunity was taken of making a comparison, using identical dosage and test methods, with this vitamin-B_{12}–peptide in similar patients.

Materials and Methods

Seventeen consecutive cases of pernicious anaemia in relapse were studied. The diagnostic criteria included macrocytic anaemia, megaloblastic erythropoiesis, histamine-fast achlorhydria, absence of steatorrhoea or other known cause of megaloblastic anaemia. All had serum-vitamin-B_{12} concentrations below 100 $\mu\mu$g./ml. At the start of the trial none showed any neurological mani-

festations. All the patients were treated with oral vitamin-B_{12}–peptide from the stage of relapse and completed a short-term 15-day trial. Ten of them were maintained on the same regime for a further 3–13 months. The dose of oral vitamin B_{12} given as B_{12}–peptide complex was 100, 200, or 500 μg. daily. It was taken in tablet form, each tablet containing 100 μg., as a single dose early each morning. Each patient took a standard dose throughout the trial. Haematological techniques and serum-vitamin-B_{12} estimations were performed as described by Chalmers and Shinton (1958).

Results

Short-term (15-day) Studies

The changes in haemoglobin, red-cell count, packed cell volume, and serum-vitamin-B_{12} concentration after 15 days of treatment with each dose are summarized in Table I. In all of the patients there was an improvement

TABLE I.—*Pernicious Anaemia in Relapse Treated for 15 Days with Daily Oral Doses of Vitamin-B_{12}–Peptide*

Case No.	Sex and Age	Daily Oral Dose (μg.)	Hb (g./100 ml.)		R.B.C. (mil./c.mm.)		P.C.V.		Serum Vitamin B_{12} ($\mu\mu$g./ml.)	
			0*	15†	0	15	0	15	0	15
1	M 74	100	6·9	9·1	1·6	2·5	20	28	10	100
2	M 53	100	6·6	8·8	1·5	2·5	20	28	10	100
3	M 53	100	7·8	11·4	2·0	3·3	24	39	40	70
4	F 35	100	6·5	7·9	1·7	2·6	20	30	20	70
5	F 63	100	4·5	8·3	1·1	2·7	14	29	20	200
6	F 34	100	12·0	13·4	3·6	4·0	38	42	50	130
7	F 67	100	8·9	10·5	2·2	2·8	29	35	90	230
8	M 64	200	4·1	6·7	1·0	2·0	13	25	40	140
9	F 56	200	6·7	10·4	1·8	3·4	21	35	30	130
10	M 58	200	12·3	12·5	3·0	3·5	38	42	40	180
11	F 59	200	6·1	10·7	1·4	2·8	17	31	40	190
12	F 54	200	7·3	9·5	1·8	2·9	22	30	50	150
13	F 64	200	5·7	7·6	1·4	2·4	17	25	90	260
14	M 54	200	7·3	9·8	1·8	2·8	22	31	10	80
15	F 63	500	10·1	11·7	2·5	3·0	33	38	10	250
16	F 60	500	5·6	7·5	1·3	2·1	17	27	40	290
17	F 38	500	5·0	8·8	1·4	3·1	14	31	30	370

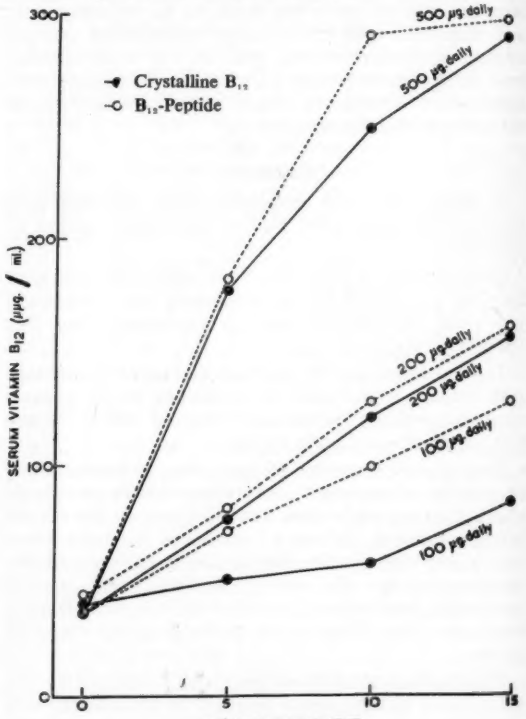
* Before treatment. † 15 days after treatment.

in their haematological values irrespective of the daily dosage received. The serum-vitamin-B_{12} level from day 0 to days 5, 10, and 15 was found to rise progressively with the corresponding increase in the daily amount of vitamin-B_{12}–peptide given. These levels were compared with those previously obtained when giving similar doses of crystalline vitamin B_{12} (Table II). Some of these results have been already reported (Cases 5–21, Chalmers and Shinton, 1958).

The mean serum-vitamin-B_{12} concentration of all patients on days 0–15 for each respective preparation and dosage showed a progressive rise (see Chart), but when doses of only 100 μg. daily were given there was a greater increase of these levels in those patients receiving the peptide preparation compared with those receiving an equivalent dose of crystalline vitamin B_{12}. An analysis of variance was therefore carried out on all these figures in order to extract the variations due to individual patients and to the rate of rise from day 0 to day 15. From the residual variance the significance of the overall rise in each group was assessed (Table III). From this it can be seen that the difference in the vitamin-B_{12} levels between the two preparations when administering 100 μg. daily is significant, whereas with both 200 and 500 μg. daily no significant difference was found.

Maintenance Studies

Ten patients continued taking daily oral doses of the vitamin-B_{12}–peptide preparation from the stage of



Mean serum-vitamin-B_{12} values in relation to the daily oral dose of crystalline vitamin-B_{12} and vitamin-B_{12}–peptide during the first days of treatment.

TABLE II.—*Rise in Serum-Vitamin-B_{12} Concentration (μg./ml.) from 0 to 15 Days in Cases of Pernicious Anaemia in Relapse Treated by Two Oral Preparations of Vitamin B_{12}*

		Vitamin-B_{12}–Peptide Complex								Crystalline Vitamin B_{12}									
	Case No.:	1	2	3	4	5	6	7	Mean	5	6	8	22	23	24	25			Mean
100 μg. daily	Day 0	20	10	40	20	20	50	90	35	50	15	20	10	20	60	30			30
	,, 5	40	20	40	20	120	80	150	70	50	30	30	20	40	130	40			50
	,, 10	80	50	50	30	150	120	210	100	50	60	50	40	50	160	40			60
	,, 15	100	100	70	70	200	130	230	130	75	85	60	40	80	160	70			80
	Case No.:	8	9	10	11	12	13	14		11	12	13	26	27	28	29	30	31	
200 μg. daily	Day 0	40	30	40	40	50	90	10	40	20	30	30	40	40	30	10	30	60	30
	,, 5	70	40	110	80	70	140	40	80	40	60	40	70	60	70	90	100	140	70
	,, 10	100	80	150	170	130	180	70	130	60	150	50	80	120	110	110	110	260	120
	,, 15	140	130	180	190	150	260	80	160	90	180	90	160	160	170	180	120	260	160
	Case No.:	15	16	17						14	15	16	17	18	19	20	21		
500 μg. daily	Day 0	10	40	30					30	25	20	35	30	30	20	50	30		30
	,, 5	160	200	180					180	190	200	180	310	150	170	150	110		180
	,, 10	230	280	360					290	230	240	260	430	230	220	230	150		250
	,, 15	250	290	370					300	260	280	280	490	260	260	250	210		290

relapse for periods varying from 3 to 18 months (Table IV). All but one of those receiving 100 μg. daily (Cases 3–7) showed normal haematological values within two months, and these were maintained throughout the time of study. The exception (Case 4) failed to reach normal values after three months' therapy, and was therefore given intramuscular injections of 250 μg. of crystalline vitamin B_{12} every two weeks. Two months later a complete remission resulted.

All the patients receiving 200 and 500 μg. daily reached and maintained haemoglobin, red-cell counts, and packed cell volumes within the normal range. The serum-vitamin-B_{12} levels in each dosage group were broadly similar to those found on the 15th day of the study. Of those receiving 100 μg. daily, only Case 4 showed any appreciable difference in level after three months' therapy, the levels ranging at the end of the trial from 80 to 260 μμg./ml. In the three cases receiving 200 μg. daily (Cases 8, 9, and 10) rises after 15 days were only small, the figures ranging from 160–170 μμg./ml. after periods of three to nine months. A progressive rise for three months was found in the two patients (Cases 15 and 16) receiving 500 μg. daily, in both cases the levels being maintained around 400 μμg./ml. for a further 18 months. One patient (Case 9) who received 200 μg. daily developed peripheral neuritis in the upper limbs after three months' therapy and was therefore changed to intramuscular injections. The remainder of the patients developed no abnormal neurological signs or symptoms.

Discussion

For an oral preparation of vitamin B_{12} to be accepted as a satisfactory form of treatment of pernicious anaemia it must be established that it will reliably cause a complete clinical and haematological remission which will be maintained. It would also be desirable for it to be capable of replenishing the body stores, which are mainly in the liver. When there is a deficiency of the vitamin, the levels in the liver are similar to those in the plasma (Grasbeck, 1959), and it is therefore reasonable to assume that low serum levels in all circumstances reflect a deficiency in the body stores. If this is accepted, satisfactory treatment of pernicious anaemia also requires that the serum-vitamin-B_{12} concentration should be at least within the normal range and preferably up to the mean level of about 400 μμg./ml. (Shinton, 1959). The importance of maintaining a normal serum-vitamin-B_{12} level in patients receiving oral treatment has been emphasized by reports that where relapse is about to occur decline in this level precedes that of other haematological values (Bastrup-Madsen, 1957; Killander, 1957; Kristensen *et al.*, 1957; Lowenstein *et al.*, 1957; Blackburn *et al.*, 1959).

Furthermore, the development of neurological manifestations has been described in patients maintained on oral preparations with serum levels of 50–150 μμg./ml. (Bastrup-Madsen, 1957; Kristensen *et al.*, 1957; Varadi and Elwis, 1960). The peripheral neuritis that developed in one patient of the present series where the serum vitamin B_{12} was 170 μμg./ml. was probably another example of this danger. Regular estimations of serum-vitamin-B_{12} levels must therefore be made when an oral preparation is being used.

The claims by Mooney and Heathcote (1960, 1961) that vitamin-B_{12}–peptide is superior to crystalline B_{12} in the oral treatment of pernicious anaemia were based on therapeutic trials in four cases where one preparation followed the other without interval. The responses observed while the patients were receiving the vitamin B_{12}–peptide could therefore have been a carry-over effect of the crystalline vitamin B_{12} given primarily, such a delayed response having been previously reported (Chalmers and Shinton, 1958). However, in the present investigation it has been shown that when 100 μg. daily of crystalline vitamin B_{12} or its equivalent dose of vitamin-B_{12}–peptide is given to individual but similar groups of cases there is a greater rise in the mean serum-vitamin-B_{12} level in those receiving the peptide complex. This concurs with the demonstration by Milhaud (1961) that in patients who have had a partial gastrectomy the absorption of radioactive vitamin B_{12} in small doses was greatly increased when given in the form of a peptide complex.

These considerations, while of academic interest, have little bearing on the possible therapeutic advantages of vitamin-B_{12}–peptide, as, like the crystalline form, it is necessary to give a daily dose of at least 200 μg. in order to be sure that the serum-vitamin-B_{12} level is being maintained near the normal mean. At this dosage no difference was found between the two preparations. There may be special circumstances where oral treatment of pernicious anaemia is desirable (*Brit. med. J.*, 1959), but in the routine management of these patients the view previously expressed by Chalmers and Shinton (1958) remains that intramuscular injections of vitamin B_{12} provide the most reliable method, ensuring a rapid response, and maintenance free of the risk of neurological complications.

TABLE III.—*Residual Variances Between Serum-Vitamin-B_{12} Concentrations After Treatment with Vitamin-B_{12}–Peptide as Compared with Crystalline Vitamin-B_{12}*

Daily Dosage	Variance Ratio	Degrees of Freedom	P
100 μg.	36	1/36	⩽0·001
200 ,,	1·4	1/42	>0·2
500 ,,	1·0	1/27	>0·2

TABLE IV.—*Long-term Maintenance Therapy with Daily Oral Doses of Vitamin-B_{12}–Peptide*

Case No.	Values at Beginning of Trial				Daily Oral Dose (μg.)	Months of Treatment	Values at End of Trial			
	Hb (g./100 ml.)	R.B.C. (mil./c.mm.)	P.C.V. (%)	Serum Vitamin B_{12} (μμg./ml.)			Hb (g./100 ml.)	R.B.C. (mil./c.mm.)	P.C.V. (%)	Serum Vitamin B_{12} (μμg./ml.)
3	7·8	2·0	24	30	100	6	13·8	4·7	43	80
4	6·5	1·7	20	20	100	3	10·2	4·2	35	140
5	4·5	1·1	14	30	100	3	12·4	4·7	41	200
6	12·0	3·6	38	60	100	18	11·5	3·6	37	170
7	8·9	2·2	29	90	100	6	13·1	4·6	43	260
8	4·1	1·0	13	40	200	3	13·6	4·6	41	160
9	6·7	1·8	21	40	200	9	15·2	5·0	46	170
10	12·3	3·0	38	40	200	5	14·6	4·8	44	160
15	10·1	2·5	33	10	500	18	13·3	4·5	39	420
16	5·6	1·3	17	40	500	18	13·7	4·6	40	390

Summary

The use of vitamin-B_{12}–peptide as a possible form of oral treatment for pernicious anaemia has been assessed clinically, haematologically, and by serum-vitamin-B_{12} estimations.

While it has been shown to be similar in effect to crystalline vitamin B_{12} when given orally in doses of 200 μg. daily or more, with 100 μg. daily there is a comparatively greater rise of the serum-vitamin-B_{12} level over 15 days.

Parenteral therapy remains the most reliable method of treating pernicious anaemia, but should this be contra-indicated then generous daily doses of either crystalline vitamin B_{12} or vitamin-B_{12}–peptide are as effective as any other form of oral therapy yet developed.

I thank the physicians who referred cases to me for these trials; the patients for their co-operation; Dr. J. A. H. Waterhouse for help with the statistical analysis; Dr. J. N. Marshall Chalmers for his co-operation and advice; Mr. C. I. D. Wilson for technical assistance; and Distillers Co. (Biochemicals) Ltd. for supplying the vitamin-B_{12}–peptide.

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Dr. C. S. P. HAMILTON, of Glenageary, Eire, has presented a pewter medal to the Maritime Institute Museum, Dun Laoghaire. The medal was one of a number presented to the crew of the British sloop *Calliope* by the citizens of Apia on the occasion of the hurricane which struck Apia and wrecked several German and American warships in 1889. The *Calliope* was the only ship to sail for the open sea when the hurricane struck. The others threw out extra anchors and attempted to ride out the storm. Some foundered and others were driven ashore. When the *Calliope* returned after the hurricane her Irish commander, Captain Kane, and his crew set to work to bring order out of the destruction in the harbour. In gratitude for their efforts and in admiration of Captain Kane's superb seamanship, the leading residents of Apia gave the captain a silver medal, and each member of the crew a pewter medal. One of these pewter medals, which was given to an Irish sailor, eventually came into the possession of Dr. Hamilton. (*New Zealand News.*)

HAEMOGLOBIN Q-ALPHA-THALASSAEMIA

BY

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Three years ago a new haemoglobin, Q, was described by Vella, Wells, Ager, and Lehmann (1958); it was found in combination with haemoglobin H. Since then there has been much progress in our knowledge of the fine structure of haemoglobin, which we owe largely to Ingram, Schroeder, Itano, and their colleagues. The present paper describes the case of a child in whom haemoglobin Q was found together with haemoglobin Bart's. Taken together with the previous case (Vella *et al.*, 1958), and utilizing the new information on the structure and inheritance of human haemoglobin, our findings make it possible to define a new syndrome—Hb Q-α-thalassaemia.

Case Report

A 10-months-old boy from Thailand, who had developed severe atopic eczema at the age of 7 months, was admitted to the Hospital for Sick Children for treatment. Apart from the eczema, physical examination revealed no abnormal findings; examination of the blood film, however, showed numerous target cells, and further investigations were therefore carried out.

Laboratory Investigations

The results of routine laboratory investigations are summarized in the Table. A stained blood film (Fig. 1, A) showed considerable hypochromia, moderate anisocytosis and poikilocytosis, and many target cells. Except for an eosinophilia, the white cells and platelets were normal. On supervital staining with brilliant cresyl blue a moderate number of red cells were found to contain inclusion bodies (Fig. 2), similar to those found in cells containing haemoglobin H. Red-cell osmotic fragility was greatly diminished, as shown in Fig. 3. The direct Coombs test was negative. The serum bilirubin was 0.2 mg./100 ml. and serum-protein electrophoresis was normal.

The combination of a high serum-iron level with a hypochromic blood picture suggested a diagnosis of thalassaemia. On examination of the haemoglobin by paper electrophoresis at alkaline *p*H three fractions were observed; the fastest, comprising about 5%, moved in the position of Hb Bart's; the second and major component was found just behind Hb A, in the position of Hb Q; and the third, which amounted to 2% of the whole, was just behind the position of Hb A_2 (Fig. 4). Hb A and Hb A_2 themselves were not found. The finding of Hb Bart's was confirmed by paper electrophoresis at acid *p*H. On chromatography in "amberlite IRC 50" at *p*H 6, no Hb A was discovered, and the major component again moved in the position of Hb Q. Hb F was not found, although 2.4% alkali-resistant haemoglobin was shown to be present by the one-minute alkali-denaturation test (Singer, Chernoff, and Singer, 1951). This was explained by the presence of 5% Hb Bart's, which is about half as resistant to alkali as Hb F in this test (Ager and Lehmann, 1958). In several experiments Hb H was not discovered on electrophoresis, although the inclusion bodies (Fig. 2) suggested that some had been present. However, in one experiment with large amounts of very

Results of Routine Laboratory Investigations

Subject	Red Cells (mill./c.mm.)	Hb (g./100 ml.)	P.C.V. (%)	M.C.V. (c.μ)	M.C.H. (μμg.)	M.C.H.C. (%)	M.C.D.* (μ)	Reticulocytes (%)	Osmotic Fragility	Inclusion Bodies	Serum Iron (μg./100 ml.)	Total Iron-binding Capacity (μg./100 ml.)	Haemoglobins
Propositus	5·55	9·6	35	62·5	31·4	27·4	6·2	5	Greatly reduced	Present	226	350	Q, Bart's Q_2 (+H)
Father ..	—	14·4	47	—	—	29·5	6·6	1·4	Slightly reduced	None	62	200	A, Q, A_2, Q_2
Mother ..	5·0	12·2	41	82	24·4	29·7	6·5	1·8	Reduced	A few	188	320	A, A_2 (+H)

* Derived from a Price-Jones curve.
The findings in the father are explained on the basis of iron deficiency, and in the propositus and mother on the basis of thalassaemia.

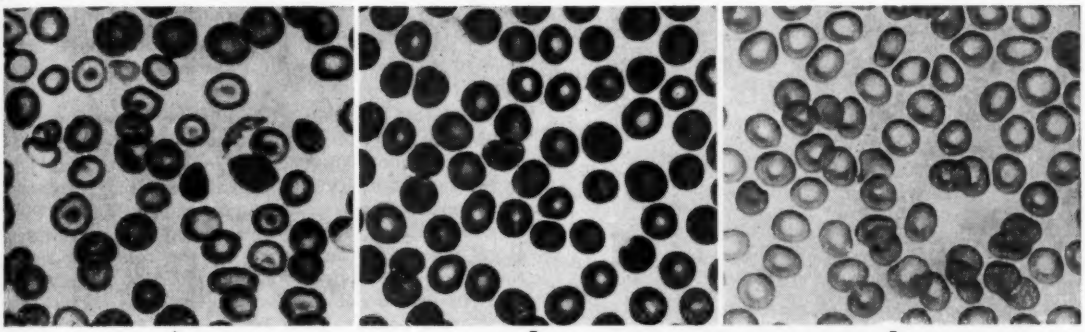

FIG. 1.—Red cells stained with eosin. (×650.) A, Propositus. B, Father. C, Mother.

fresh haemolysate, a small trace of haemoglobin was discovered in the position of Hb H; this could only have amounted to much less than 0.5% of the total.

Investigation of the Parents

The father was 34 years old and healthy, and physical examination showed no abnormality. His father had died in old age, and his mother, aged 81, was well; his five sisters and one brother were all alive and well.

The results of routine laboratory investigations are summarized in the Table. The blood film (Fig. 1, B) was normal and no red-cell inclusion bodies were seen in cresyl-blue-stained films. Red-cell osmotic fragility (Fig. 3) was only slightly diminished and the direct Coombs test was negative. The serum bilirubin was 0.1 mg./100 ml. There was no detectable alkali-resistant haemoglobin, and on paper electrophoresis at alkaline *p*H two major fractions were seen in the positions of Hb A and Hb Q; on staining, these were seen as a confluent broad band (Fig. 4). Hb A_2 was present (2%), and an additional band was seen just behind the Hb A_2, in the position of the abnormal minor component of the propositus. The slight reduction in both M.C.H.C. and red-cell fragility could be explained on the basis of a mild iron deficiency; the low serum iron is also in favour of this. Further investigation of the father was not possible, however, as he failed to co-operate.

The mother, aged 28, was well; her parents were both alive and healthy, as were her three brothers and four sisters. The stained film showed slight hypochromia, anisocytosis, and poikilocytosis (Fig. 1, C); the white cells and platelets were normal. Films stained supravitally with brilliant cresyl blue showed a few red-cell inclusion bodies. Red-cell osmotic fragility (Fig. 3) was moderately diminished. The direct Coombs test was negative. Examination of the haemoglobin showed nothing abnormal (Fig. 5), and, although the inclusion bodies had indicated the presence of Hb H, this was not present in sufficient quantities for demonstration by paper electrophoresis.

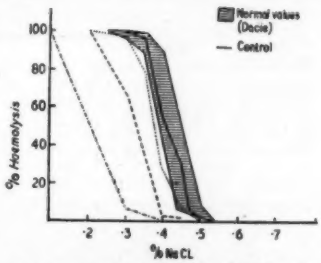

FIG. 3.—Red-cell osmotic fragility (in saline at 20° C.) of propositus, father, and mother. . . . .=Father. - - - -= Mother. -.-.-=Child.

FIG. 2.—Inclusion bodies from Hb H demonstrated by supravital staining with brilliant cresyl blue.

Discussion

Normal adult haemoglobin (Hb A) consists of two subunits—a pair of α-chains and a pair of β-chains (Rhinesmith, Schroeder, and Pauling, 1957; Rhinesmith, Schroeder, and Martin, 1958); these chains differ in their chemical structure, and it is accepted that they are controlled by different genes. Foetal haemoglobin and haemoglobin A_2 share the α_2 subunits of haemoglobin A, but in combination with γ-chains in Hb F ($\alpha_2\gamma_2$) (Schroeder and Matsuda, 1958; Hunt, 1959), and with δ-chains in Hb A_2 ($\alpha_2\delta_2$) (Stretton and Ingram, 1960; Muller and Jonxis, 1960). The principal

abnormalities of human haemoglobin production are deficiencies of the normal chains, or variations in their chemical constitution. For example, classical thalassaemia can be understood as a deficiency of the β-chain (Ingram and Stretton, 1959), hence in this an increase is seen in $\alpha_2\gamma_2$ (Hb F) and $\alpha_2\delta_2$ (Hb A_2). β-Chain thalassaemia seems to affect the β-chain production only, but not that of the β-chain variants, such as the β_2^S subunits of sickle-cell haemoglobin or the β_2^C subunits of haemoglobin C. Thus in sickle-cell thalassaemia more Hb S is formed than Hb A, and in Hb C disease more Hb C than Hb A.

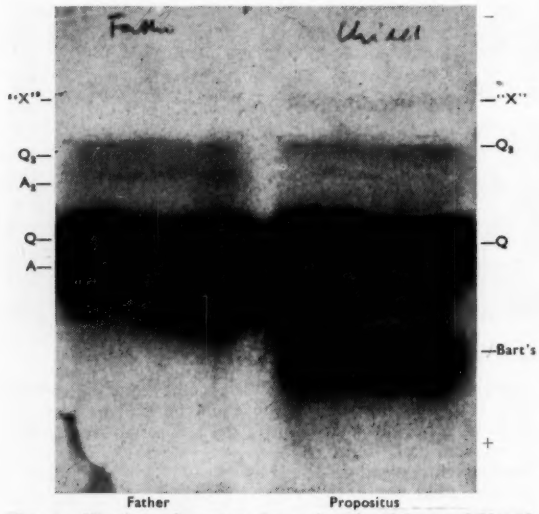

FIG. 4.—Hanging-strip paper electrophoresis of haemoglobin of father and propositus. Tris buffer *p*H 8.6. Strips stained with light green. In the father, Hb Q_2 and Hb A_2 are demonstrated; on staining, the Hb A and Hb Q merge into a single broad band. In the child, Hb Q_2, Hb Q, and Hb Bart's are demonstrated. (The uppermost stained band in each strip is not haemoglobin but the protein-X of Derrien *et al.* (1956).)

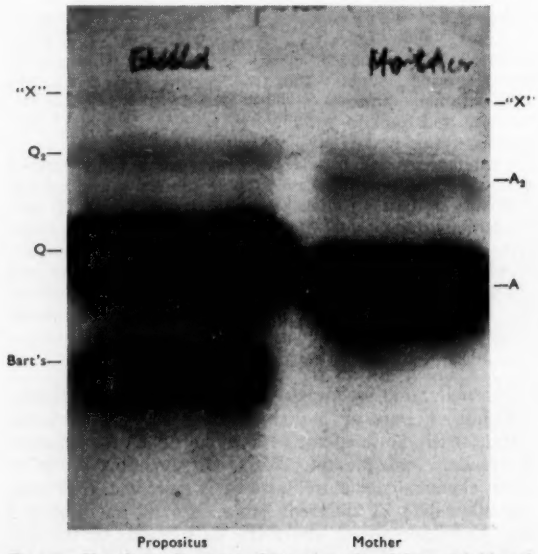

FIG. 5.—Hanging-strip paper electrophoresis of haemoglobin of mother and propositus. (Preparation as in Fig. 4.) In the mother, Hb A_2 and Hb A are demonstrated; and in the child, Hb Q_2, Hb Q, and Hb Bart's (The uppermost stained band in each strip is the protein-X of Derrien *et al.* (1956).)

Conversely, α-chain deficiency affects all three normal haemoglobins, and leads to a surplus of β_2 and γ_2 subunits—and presumably also of δ_2 subunits, although this has not yet been demonstrated. The surplus β_2 subunits will combine to form β_4 (Hb H) (Jones, Schroeder, Balog, and Vinograd, 1959), and the surplus γ_2 subunits to form γ_4 (Hb Bart's) (Hunt and Lehmann, 1959). Thus in α-chain thalassaemia a raised Hb A_2 will not be found, and it is noteworthy that Dittmann, Haut, Wintrobe, and Cartwright (1960) found that the relatives of patients with Hb H disease and a thalassaemic blood picture did not show the customary rise in the Hb A_2 fraction. We have therefore two types of thalassaemia: α-chain thalassaemia with Hb Bart's and Hb H, but low Hb A_2 and low or absent Hb F; and β-chain thalassaemia with raised Hb F and raised Hb A_2.

The father of the propositus is a symptom-free haemoglobin Q-trait carrier, and Hb Q is known to have an abnormal α-chain (Jones, Schroeder, and Lehmann; unpublished observations). In the mother a diagnosis of thalassaemia can be made on the basis of a low M.C.H. with a normal serum iron. As neither Hb F nor an increase in Hb A_2 was found, and as a trace of Hb H was probably present, this thalassaemia must be considered to affect the α-chains. The child therefore appears to have inherited Hb Q ($\alpha_2^Q\beta_2$) from the father plus an α-chain thalassaemia from the mother. In other words he has the same condition as that previously described as Hb Q-H disease—except that instead of moderate quantities of Hb H (β_4), Hb Bart's (γ_4) is found with only a very little Hb H, which we now realize has the same significance.

A particularly interesting feature in this case is the abnormal minor fraction, which, following Shooter's example, we may call Q_2 (Shooter, Skinner, Garlick, and Barnicot, 1960). Shooter and his co-workers found that Hb G was the only adult haemoglobin present in a blood sample obtained from West Africa. In this case the abnormal minor component ("G_2") moved as far behind the position of normal A_2 as Hb G moved behind Hb A. It was then found that this particular Hb G (G_{Ibadan}) had its abnormality in the α-chain (Gammack, Huehns, Shooter, and Gerald, 1961), and it was concluded that Hb G_2 was a combination of the abnormal

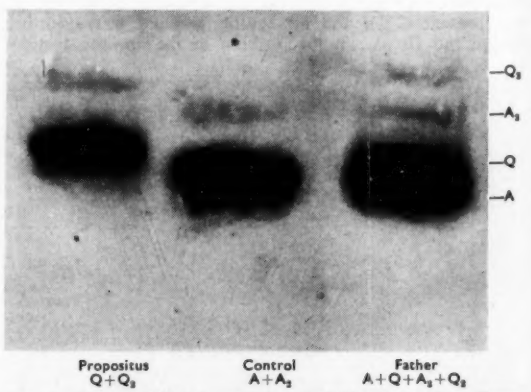

FIG. 6.—Haemoglobin A_2 and haemoglobin Q_2. After discontinuous starch-gel electrophoresis (Poulik, 1957) and staining, the gel was made transparent with glycerol (Gratzer and Beaven, 1960). To obtain the required amounts of A_2 and Q_2 larger quantities of the A+Q mixture had to be used than usual, and the rear part of the A band overlaps with the front part of the Q band.

α_2^G with the normal δ_2 of Hb A_2. The abnormal minor component in our propositus (Q_2) could be explained along the same lines as a combination of α_2^Q and δ_2—that is $\alpha_2^Q\delta_2$. Further support for this hypothesis is obtained from the observation that the father's haemoglobin contains both A_2 and another minor fraction corresponding to the child's Hb Q_2 (Fig. 6).

Summary and Conclusions

Hb Q-α-thalassaemia was found in a Thai infant. The father is an Hb-Q-trait carrier, and the mother has α-thalassaemia. An interesting feature in the child is the absence of Hb A_2 which is replaced by "Q_2"; in the father A_2 and Q_2 are present together. Taken together with a previously described case of "Hb Q-H disease" the present study establishes a new concept—Hb Q-α-thalassaemia.

We thank Sir Wilfred Sheldon, K.C.V.O., for his help in this investigation.

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ABO BLOOD GROUPS OF SIBLINGS OF GASTRIC ULCER AND GASTRIC CARCINOMA PATIENTS*

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An increased frequency of blood group O has been found in gastric ulcer patients and an increased group A frequency in gastric carcinoma patients (Buckwalter *et al.*, 1956). Blood donors were used as controls for these studies. Inadvertently, blood donors may be selected from a different stratum of the population than the patients. Differences between the blood type frequencies of the controls and patients might, in this event, reflect anthropological differences between the two strata of the population rather than cause-and-effect association between the ABO blood groups and the disease in question. By elimination of the possibility of population stratification the siblings of the patients should provide more reliable controls (Clarke *et al.*, 1956). The results of sibship studies support a cause-and-effect explanation for the association between the ABO blood groups and duodenal ulcer (Buckwalter *et al.*, 1960). This is a report of similar studies of siblings of patients with gastric ulcer and gastric carcinoma.

Methods.—The clinical material was provided by patients of the University of Iowa and Iowa City Veterans Administration Hospitals. The diagnosis was based on morphological findings in all of the gastric carcinoma patients and in two-thirds of the gastric ulcer patients; the remainder of the gastric ulcer patients had "ironclad" clinical diagnoses. The methods were the same as those used in the study of duodenal ulcer siblings. The same controls were used. In analysing gastric carcinoma sibships, A_1 and A_2 were regarded as "A" blood, while A_1B and A_2B were regarded as "non-A" blood. The sibships were also analysed after eliminating all sibs differing in sex from their propositi.

Results

The numbers and percentages of the propositi with gastric ulcer, their affected sibs, unaffected sibs, sibs whose ulcer status was unknown, and controls of each ABO blood group are recorded in Table I. Note the increase in group O frequency in propositi (I), as compared with controls (V). When the differences between the blood-type frequencies of the propositi and controls are tested for statistical significance by the chi-square method with three degrees of freedom, $0.02<P<0.05$. When all the sibs (II, III, and IV) are combined with the propositi and compared with the controls, $0.02<P<0.05$. When the method suggested by Smith is employed (Clarke *et al.*, 1956), which considers each sibship separately, an excess of group O in gastric ulcer propositi (observed) compared with that expected is noted.

In the past, when the Smith method has been used in analysing the data, the working hypothesis has been that a difference between the ABO blood group frequencies of the propositi and sibs might be found. A two-tail test has been used, based on the assumption that this difference might be either an increase or a decrease in O frequency. However, in view of the overwhelming evidence indicating an increase in blood group O frequency in peptic ulcer, and in the light of the work of Clarke *et al.*, an increase in group O frequency is to be expected. If this occurs, then the one-tail test perhaps provides a more valid measure of the significance of the observed differences. The raw data and the P values obtained when the one- and two-tail tests are used in the analysis of the gastric ulcer, and the previously published duodenal ulcer sibship data (Buckwalter *et al.*, 1960) by Smith's method, are recorded in Table II. Note the relatively high level of statistical significance found when the duodenal and gastric ulcer data are combined.

Only two of the gastric ulcer sibships segregated for group O and ulcer after the propositi were excluded. The basic data are included so that other investigators may, if they wish, combine these data with their own in examining the chance of an affected sib being group O with the propositi excluded:

O expected, 0.9286; O observed, 1.0000;
variance, 0.4949.

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The gastric carcinoma data show increases in the blood type A frequencies of the propositi (I) and in all sibs (II, III, and IV) as compared with controls (V) (Table III). These differences do not have statistical significance when tested by the chi-square method. When the method of Smith is used an excess of group A in propositi (observed) compared with that expected is noted. This difference is not statistically significant, using either the one- or the two-tail test (Table IV).

Discussion

The differences between the ABO blood type frequencies of the propositi and the controls, characterized by an increased frequency of type O in gastric ulcer and type A in gastric carcinoma, are in accordance with our previous findings. The lower level of significance in gastric ulcer and the absence of significance in gastric carcinoma, compared with the previous report, reflect the smaller number of patients in the current study. The actual differences between the patient and control blood-type frequencies are of greater magnitude in the current study.

TABLE I.—*Blood Groups of Propositi (Gastric Ulcer Patients) and Their Siblings*

Blood Type	I Propositi		II Affected Sibs		III Unaffected Sibs		IV Unknown Sibs		V Population Controls	
	No.	%	No.	%	No.	%	No.	%	No.	%
O	137	52·9	13	61·9	160	47·3	31	50·0	22,392	44·8
A	87	33·6	4	19·0	146	43·2	26	41·9	21,144	42·3
B	27	10·4	4	19·0	23	6·8	4	6·5	4,695	9·4
AB	8	3·1	0	0·0	9	2·7	1	1·6	1,748	3·5
Total	259	100·0	21	99·9	338	100·0	62	100·0	49,979	100·0

TABLE II.—*Analysis of the Chance of the Propositus Being Group O in the Sibships Segregating for Blood Group O*

	No. of Sibships	Group O Observed	Group O Expected	Variance
Gastric ulcer ..	47	28	23·4188	10·7614
Duodenal ,,* ..	96	56	46·9797	22·0082
Combined data	143	84	70·3985	32·7696

From which we obtain:

		One-tail Test	Two-tail Test
Gastric ulcer:	$\frac{28-23\cdot4188}{\sqrt{10\cdot7614}}=\frac{4\cdot5812}{3\cdot280}=1\cdot40$	0·05<P<0·10	0·10<P
Duodenal ,,	$\frac{56-46\cdot9797}{\sqrt{22\cdot0082}}=\frac{9\cdot0203}{4\cdot691}=1\cdot92$	0·02<P<0·05	0·05<P<0·10
Combined data:	$\frac{84-70\cdot3985}{\sqrt{32\cdot7696}}=\frac{13\cdot6015}{5\cdot724}=2\cdot38$	0·001<P<0·01	0·01<P<0·02

* Buckwalter *et al.* (1960).

TABLE III.—*Blood Groups of Propositi (Gastric Carcinoma Patients) and Their Siblings*

Blood Type	I Propositi		II Affected Sibs		III Unaffected Sibs		IV Unknown Sibs		V Population Controls	
	No.	%	No.	%	No.	%	No.	%	No.	%
O	37	36·3	3	60·0	123	44·4	19	35·9	22,392	44·8
A	52	51·0	1	20·0	119	43·0	29	54·7	21,144	42·3
B	10	9·8	1	20·0	20	7·2	5	9·4	4,695	9·4
AB	3	2·9	0	00·0	15	5·4	0	0·0	1,748	3·5
Total	102	100·0	5	100·0	277	100·0	53	100·0	49,979	100·0

TABLE IV.—*Analysis of the Chance of the Propositus Being Blood Group A in the Sibships Segregating for Blood Group A*

	No. of Sibships	Group A Observed	Group A Expected	Variance
Gastric carcinoma	16	12·0000	9·8810	3·5374

		One-tail Test	Two-tail Test
From which we obtain	$\frac{12-9\cdot8810}{\sqrt{3\cdot5374}}=\frac{2\cdot1190}{1\cdot881}=1\cdot13$	0·10<P	0·10<P

Since gastric ulcer sibships were selected through propositi with a high group O frequency—that is, 52.9%—a high O frequency would be expected in their sibs as well. This is borne out by our data; a similarly high O frequency in sibs was noted in the duodenal ulcer sibship study. Similarly, in gastric carcinoma, the propositi high in blood type A had siblings also high in A. These findings are consistent with the population stratification hypothesis for the association between the ABO blood groups and gastric ulcer, duodenal ulcer, and gastric carcinoma.

With Smith's method—the most and perhaps only meaningful method suggested to date for analysis of sibship data—differences between the propositi and unaffected sibs are observed which cannot be explained by population stratification and which support the cause-and-effect hypothesis. The differences between the expected and observed which are of borderline statistical significance, using either the one- or the two-tail test, are in the expected direction and are consistent with as large blood-group associations as have been found.

The finding of an increased frequency of group O in the 47 gastric ulcer sibships, similar to that observed in the 97 duodenal ulcer sibships, suggests common factors, genetic and other, for duodenal and gastric ulcer. The results of our blood-group studies showing an excess of group O in gastric ulcer provide further support for this concept. Clarke *et al.* (1955) have found no increased group O frequency in gastric ulcer patients. However, the results of their duodenal ulcer sibship and blood-group studies agree with ours (Clarke *et al.*, 1956). Differences in case selection related to diagnostic methods and criteria seem an unlikely explanation for the discrepancies between our findings and those of Clarke *et al.* in gastric ulcer. Clinical practices in Iowa and Liverpool do not greatly differ. It is unlikely that sufficient numbers of duodenal ulcer patients were inadvertently included in the gastric ulcer group in our study to cause the observed discrepancy. It is more likely that the discrepancy is due to chance. Studies as large as the Liverpool one can easily give a negative result for an association of the magnitude suggested for gastric ulcer based on data collected by 1957 (Roberts, 1957b). Sibling studies in the Liverpool gastric ulcer patients would be of interest in view of the above.

Assuming that dupdenal and gastric ulcer are related diseases with common genetic and other factors, we combined our sibship data. Better justification for combining the duodenal and gastric ulcer data for analysis (Roberts, 1961, personal communication) is that an excess of blood type O is expected in each disease. By combining and analysing the data, the excess of O in the propositi, compared with their unaffected sibs, appears to be definitely significant statistically (Table II). This provides additional support for the cause-and-effect explanation for the association of ABO blood group and peptic ulcer.

Perhaps the strongest factor influencing the incidence of peptic ulceration is sex. This variable has been removed in analysing the data by a method suggested by Roberts (1957a) (Table V). When the sibs of the sex opposite to that of the propositi are eliminated, the number of sibships which may be used in the analysis is reduced. Note, however, that in both duodenal and gastric ulcer the observed frequency of group O still exceeds that expected, although the probabilities are lower than in the previous analysis, in which sex was not considered.

The mean age of patients with gastric carcinoma is much higher than that of those with peptic ulceration. Because of fewer numbers of surviving sibs, the accumulation of sibship data is more difficult. Excesses of group A were noted when the propositi were compared with the unaffected sibs and with the population controls. An excess of A was also found in the propositi of the 16 sibships segregating for group A. None of these differences were of statistical significance. All that may be said is that these data are consistent with the causal explanation for the association of blood group and carcinoma of the stomach. The most important reason for publishing these data is to make them available for the use of other investigators in evaluating their findings.

TABLE V.—*Analysis of the Chance of the Propositus Having Group O in the Sibships Segregating for Blood Group O After Sibs of the Sex Opposite that of the Propositus are Removed*

	No. of Sibships	Group O Observed	Group O Expected	Variance
Gastric ulcer ..	32	19	15·8166	7·7051
Duodenal ,,* ..	65	35	29·9413	15·2293
Combined data	97	54	45·7579	22·9344

From which we obtain:

		One-tail Test	Two-tail Test
Gastric ulcer:	$\frac{19-15\cdot8166}{\sqrt{7\cdot7051}}=\frac{3\cdot1834}{2\cdot776}=1\cdot15$	$0\cdot10<P$	$0\cdot10<P$
Duodenal ,,	$\frac{35-29\cdot9413}{\sqrt{15\cdot2293}}=\frac{5\cdot0587}{3\cdot902}=1\cdot30$	$0\cdot05<P<0\cdot10$	$0\cdot10<P$
Combined data:	$\frac{54-45\cdot7579}{\sqrt{22\cdot9344}}=\frac{8\cdot2421}{4\cdot789}=1\cdot72$	$0\cdot02<P<0\cdot05$	$0\cdot05<P<0\cdot10$

* Buckwalter *et al.* (1960).

Conclusions

Evidence is presented of an increased frequency of blood group O in gastric ulcer patients, in the siblings of gastric ulcer patients, and in the patients as compared with their siblings.

These data have been combined with the previously published duodenal ulcer findings, which show similar increases in O frequency. Additional support for a causal explanation of the association of the ABO blood groups with peptic ulceration is provided.

The findings in the gastric carcinoma sibship study, based on fewer data, are less convincing, but show an excess of blood group A in patients, their siblings, and in the patients compared with their siblings.

The original manuscript was reviewed by Dr. J. A. Fraser Roberts. The reader has thereby been provided with a more critically reasoned and precisely stated report of our findings. We are fully responsible for the shortcomings of this report.

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The North of England Industrial Health Advisory Service is publishing a *Bulletin* two or three times a year and will send it to all member firms. The service is sponsored jointly by local management, the Trades Union Council, and King's College, Newcastle upon Tyne, and its headquarters are at 52 Leazes Terrace, Newcastle upon Tyne 1.

Medical Memoranda

Case of Adder-bite with Thrombosis of the Saphenous Vein

The noxious effects of adder-bite are usually insignificant compared with the fear and alarm engendered by such an occurrence. Nevertheless, venom from *Vipera berus* may place the life of a child in jeopardy, as described below.

CASE HISTORY

At 7 p.m. on June 21, 1960, a healthy 5-year-old boy living in a remote rural area of Argyll complained of a painful and swollen left ankle. It was discoloured and flecked with blood on the medial aspect. The boy's statement that his ankle had been injured "in a door" was believed. One hour later he began to vomit, and this continued intermittently for 24 hours. By 10 p.m. the discoloration had spread from the ankle to mid-thigh, and the child was delirious and in considerable pain.

Next day he was seen by a local practitioner, who sent him to the West Highland Hospital, Oban, some 30 miles (48 km.) distant. At this point he admitted having been bitten by a "big worm" while engaged with his brother in the strictly forbidden sport of trying to throw a snake on to the roof of the cottage. The boy was given 100 mg. of hydrocortisone and transferred by ambulance to the Royal Hospital for Sick Children, Glasgow, where he was admitted at 5 p.m. on June 22. Prior to his arrival antivenin had been obtained from Edinburgh.

On admission he was profoundly shocked and restless, with a very striking and persistent head-shaking movement. He was mentally confused and markedly dehydrated. The radial pulses were not palpable. The blood-pressure could not be recorded, and the heart sounds were rapid and of very poor quality.

The entire left leg was grossly swollen, the skin being tense, shining, mottled dark blue, purple, and yellow, with a sharp line of demarcation just below the inguinal ligament. Neither the femoral nor any other arterial pulse could be felt in the left leg or foot. Two small puncture wounds were visible on the medial aspect of the ankle, and the long saphenous vein was thrombosed.

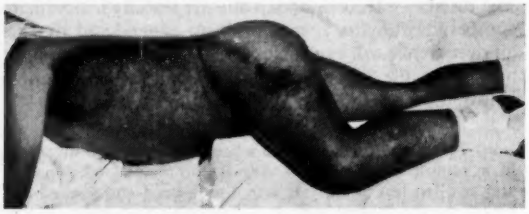
Resuscitation and treatment for shock were carried out promptly in the form of intravenous infusion with injection of promethazine hydrochloride and adrenaline. Sedation was given by the use of intramuscular paraldehyde. The general condition improved rapidly and the systolic blood-pressure reached 130 mm. Hg. Intramuscular penicillin and oral tetracycline were started and continued. A small incision was made at the area of the bite, and 5 ml. of antivenin (Pasteur Institute E.R. serum) infiltrated locally. A further 5 ml. was injected intramuscularly into the opposite thigh.

Next morning (June 23) he was no longer shocked and was hydrated. Mental confusion persisted, with repetitive shaking of the head, and he appeared to be in great pain. The affected leg was enormously swollen with no palpable arterial pulsation present. Two injections of hyaluronidase were given into the thigh, but these were followed by only a minor transient diminution in the circumference of the limb.

By June 24 the discoloured area had crept above the inguinal ligament and the leg was cold. The boy was still confused, and his blood urea had risen to 83 mg./100 ml. Seventy-two hours after the adder-bite (and after much consideration) an injection of 5,000 units of chymotrypsin was given intramuscularly into the opposite thigh. This resulted in three things: (*a*) a brisk general reaction causing mild shock occurred 30 minutes after the injection and lasted one hour; (*b*) the area of inflammatory swelling and tissue discoloration spread from the left iliac fossa to the left

axilla (see photograph); and (*c*) swelling and tension in the left leg decreased, and in 12 hours the femoral pulse was palpable.

From this time onward the state of the leg improved. However, the general condition of the boy deteriorated sharply; the abdominal and thoracic walls on the left side were now swollen and acutely painful, and were held immobile. On June 28 an extensive left-sided pneumonia



Photograph taken 12 hours after an injection of chymotrypsin.

developed, apparently hypostatic in type, despite the efforts which had been made to alter the patient's position frequently so far as the pain would permit, and despite the prophylactic treatment with penicillin and tetracycline. The pneumonia responded fairly quickly to chloramphenicol, and by July 8 the boy was up, running about, and threatening destruction to the adder population of Argyll.

DISCUSSION

The bite of the adder (*Vipera berus*) is seldom dangerous to the adult, and is usually just reward for interfering with this shy and non-aggressive reptile. The average adult receiving such a bite will suffer immediate pain, swelling, and discoloration locally, and perhaps transient giddiness. Only if vomiting and progressive shock appear over a period of hours does the use of antivenin locally or otherwise appear to be desirable. Analgesic and antihistaminic treatment is recommended (Morton, 1960). Death, when it occurs, usually takes place 6 to 60 hours after envenomization (Walker, 1945).

In the present instance delay aggravated the initial severity of the bite as judged by extensive local and systemic reaction and the involvement of the saphenous vein in a small child. Once the severe shock from which the boy suffered had been overcome the principal concern was for his leg, which was little improved by the injections of antivenin or of hyaluronidase. Tryptic extracts were tried as a last resort.

It has been stated (U.S. Dispensatory, 1955) that the venom of viperines is irreversibly combined with tissues within a few hours of a bite. Injection of chymotrypsin produced a reaction which strongly suggested that venom may have been released and was still active. No further antivenin was given, because further profound shock did not occur, and the risk of anaphylaxis following a second injection of antivenin seemed considerable.

Prior to May, 1961, the last recorded death from snake-bite in Great Britain occurred in 1941, and the last death from reaction to antivenin serum in 1957 (Morton, 1960).

Having been called upon to deal with this acute emergency at short notice has made us aware of the following important points brought out by the lucid contributions of Morton (1960), Birch (1959), and Manson-Bahr (1957): (1) When adder-bite occurs one should not incise locally and attempt to suck out venom or apply a tourniquet. (2) When envenomization has been considerable, vomiting followed by shock is likely to occur within a few hours of the bite. Resuscitative measures and treatment with antihistamines initially, followed by antivenin if necessary (and available), are then indicated. Anaphylaxis as a possible complication must be anticipated. (3) The condition is always apt to be more dangerous in a child.

Enthusiasm should be tempered with reason when treatment is given. It seems a simple and obvious precaution that antivenin should be available *locally* in rural areas of Scotland where *Vipera berus* is present.

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A Second Chinese Family with Haemoglobin Q

Haemoglobin Q was discovered in a Chinese man in Singapore (Vella, Wells, Ager, and Lehmann, 1958) who was suffering from a haemoglobinopathy, haemoglobin Q being associated with haemoglobin H. The same haemoglobin was then found in his mother, in whom it was present as a simple trait (A + Q).

Haemoglobin Q has not been found since, and we therefore consider it worth while recording a second observation made in Singapore in 1960. On this occasion the haemoglobin Q was accidentally found in a 9-year-old Chinese boy who was admitted to hospital with anaemia, fever, and jaundice. As a haemoglobinopathy was one of the possible diagnoses the haemoglobin was examined and found, on paper electrophoresis at *p*H 8.6, to consist of two barely separable fractions—the front one in the position of haemoglobin A

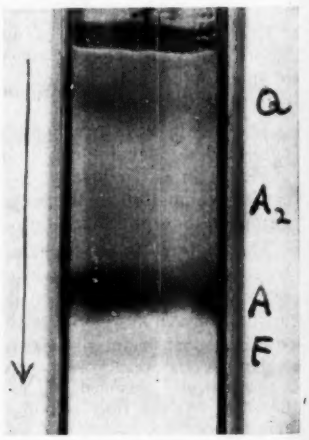

FIG. 1.—Chromatography on IRC 50 resin at *p*H 6 of the child's haemoglobin, showing haemoglobins F, A, A_2, and Q.

FIG. 2.—Paper electrophoresis barbiturate buffer, *p*H 8.6, of the haemoglobin of the patient (A+Q), his sister (A only), and his mother (A+Q).

and the rear one moving faster than G. On IRC 50 resin chromatography at *p*H 6 the wide separation typical for Q could be demonstrated (Fig. 1). Haemoglobin A_2 was not increased and the one-minute alkali denaturation test demonstrated less than 2% alkali-resistant haemoglobin. There was a very small amount of haemoglobin in the position of haemoglobin F seen on chromatography. These findings demonstrated the simple Q trait (A+Q) and were not thought to be related to the boy's illness.

The child was given a blood transfusion of 250 ml. of whole blood and progressed well. Three weeks after his admission his haemoglobin was 9.8 g./100 ml. and the jaundice had totally disappeared.

The boy's father had died of unknown causes, and it was possible to obtain blood only from the boy's mother and one of his sisters. The mother again was a case of haemoglobin A+Q, and in the sister nothing abnormal was seen (Fig. 2).

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REFERENCE

Vella, F., Wells, R. H. C., Ager, J. A. M., and Lehmann, H. (1958). *Brit. med. J.*, **1**, 752.

Spontaneous Delivery of Central Placenta Praevia

In general practice the opportunity rarely arises of witnessing the natural course of delivery in the case of a central placenta praevia. According to Gibberd (1951), "in exceptional cases of central placenta praevia the afterbirth may be delivered in front of the foetus, but it must be very unusual for this amount of placental separation to occur and for the mother to survive the haemorrhage." The following case is reported because under conditions far from ideal a mother survived the course of events set forth by Gibberd.

I must first describe the local geography of my practice, because this had a considerable bearing on the conduct and course of the case. The practice covers an area of about 600 square miles (1,550 sq. km.) around a large bay in the north of Newfoundland. Communications are poor. Mud makes the roads impassable in the spring. The sea, our main travel route, is often blocked by ice drifting in from the Arctic. The nearest hospital with facilities for blood transfusion is 130 miles (210 km.) away.

CASE REPORT

At 5.30 one morning I was called to see a young woman living in a settlement some 15 miles (24 km.) from my clinic. It was stated that she had been losing blood per vaginam for four days, that she was then having labour pains, and that the loss was increasing. I made my way through the ice, arriving in the settlement three hours later.

The patient, aged 22, was in the 36th week of her second pregnancy. She had one child, a girl, delivered normally at full term, weighing 7½ lb. (3,400 g.). In this second pregnancy she had had a threatened abortion at 10 weeks, but had retained the pregnancy. She had been seen on three occasions subsequently, and had been well.

On examination she was seen to be very pale; the pulse was 110 and regular, and the B.P. 120/80. Pregnancy was judged to be at term. The foetal heart was not heard and the foetal head was above the pelvic brim. Strong uterine contractions were occurring every three to five minutes. There was a slight vaginal loss of blood and about 1 pint (570 ml.) of clotted blood had been passed four hours previously.

It was decided to fly the patient to hospital as quickly as possible, since by this time the ice had closed in, and no further move could be made by sea. Morphine ¼ gr. (16 mg.) was given subcutaneously with the object of slowing labour until the patient could be taken to hospital. A telegram was sent for the air ambulance and the husband was asked to make a stand for the intravenous-fluid bottle. He did this very well. It was considered that help would not arrive for six hours, an estimate which proved to be over-optimistic.

The condition of the patient did not deteriorate, although some blood was still being lost vaginally. The force and frequency of the contractions diminished greatly, and she slept well. Pethidine 100 mg. was given at 11.30 a.m., and repeated two and a half hours later. During this time the weather was worsening, and by 2.30 p.m. it was obvious that no aircraft would be able to fly in. It was therefore decided that the patient should be allowed to resume labour despite the hazard. This decision was reinforced by a sudden deterioration in her condition, the B.P. falling to 80/60 and the pulse rate rising to 130 with increased vaginal loss of blood.

The patient went into strong labour and soon the placenta was seen presenting at the introitus. Intravenous administration of dextran was started and preparations were made for an immediate forceps delivery of the aftercoming foetus. But at 5.30 p.m. a stillborn child was delivered spontaneously within the complete membranes and with the placenta closely applied about the vertex. The placenta had been compressed peripherally to the thickness of about ½ in. (1.3 cm.) and was intact. Post-partum loss was about 6 to 8 oz. (170 to 230 ml.).

By this time, however, the mother was very shocked, pulse 130, B.P. 60/?. Ergometrine, 0.5 mg., was given into the intravenous tube. The uterus contracted firmly and there was no further abnormal loss per vaginam. Morphine ¼ gr. (11 mg.) and benzathine penicillin (600.000 units) were given. The mother's condition was poor, but it did not deteriorate until six hours later, when, after 2½ pints (1.4 litres) of dextran had been given, she developed left ventricular failure. This was treated with 0.5 mg. of digoxin, given with the intravenous fluid, which was then discontinued; 0.5 mg. of digoxin was given by mouth. Her condition improved until by daybreak she was no longer in cardiac failure.

She remained fairly well during the next day. Haemoglobin was estimated to be about 40%, B.P. 110/70–120/80, pulse 100, regular. The weather continued to prevent flying, and it was not until 42 hours after her delivery that she could be taken to hospital. In hospital she was given 3 pints (1.7 litres) of whole blood, and made an uncomplicated recovery. She was discharged after 12 days and has since remained well.

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REFERENCE

Gibberd, G. F. (1951). *Textbook of Midwifery*, 5th ed., p. 377. Churchill, London.

The Mental Health Research Fund's publicity for the next few months will aim at raising funds for research into schizophrenia, an illness which presents the largest single problem in its field. In support of the publicity a pamphlet has been produced to explain this illness in everyday terms. Pamphlets on other major mental illnesses will be produced later. The Fund's address is 39 Queen Anne Street, London W.1 (WEL 1272).

Reviews

PROGRESS IN TROPICAL MEDICINE

Recent Advances in Tropical Medicine. By Sir Neil Hamilton Fairley, K.B.E., M.D.(Lond.), D.Sc.(Melb.), F.R.C.P., F.R.A.C.P., D.T.M.&H.(Eng.), F.R.S., Hon.F.R.C.P.(Ed.), Hon.M.D.(Adel.), Hon.LL.D.(Melb.), Hon.D.Sc.(Syd.), A. W. Woodruff, M.D.(Durh.), Ph.D.(Lond.), F.R.C.P., D.T.M.& H.(Eng.), and J. H. Walters, M.D.(Camb.), F.R.C.P., Lieutenant-Colonel I.M.S.(Ret.). 3rd edition. (Pp. 480+viii; illustrated. 50s.) London: J. and A. Churchill Ltd. 1961.

This excellent book has been eagerly awaited in the tropical field and deserves a warm welcome.

During the past forty years the *Recent Advances* series of Messrs. Churchill has drawn the attention of practitioners to well-authenticated advances in most branches of medicine. Regular replacement in successive editions of generally accepted methods and views by sound recently published work has been a feature of the series. *Recent Advances in Tropical Medicine* is, however, atypical. No new edition has appeared since 1929 when Sir Leonard Rogers completed the second.

As the term "Tropical Medicine" covers a very wide field, embracing, as it does, clinical medicine, hygiene and preventive medicine, genetics and zoology, it may seem surprising that, in making this book a team effort, the publishers have confined their choice of writers to bedside workers; but the three distinguished physicians responsible for this edition have each a valid claim to wide knowledge and experience beyond the confines of hospital wards.

The claim in the introduction that progress in tropical medicine has been more rapid in the past fifteen years than in any other branch of medical science would not be accepted by workers in other fields—notably in endocrinology. The synthetic antimalarials, diethylcarbamazine, the major antibiotics, and D.D.T. were all in use before 1946.

During the past ten years the recognition of the great significance of the zoonoses has been the major advance in tropical medicine. The past decade has been a period of reflection and consolidation with a growing realization of the truth of the adage of Horace, *Naturam expelles furca, tamen usque recurret.* It has been accompanied by a feeling of frustration at the gradual but inexorable development of resistance to insecticides and malarial prophylactic drugs on which such strong hopes for the eradication of disease were pinned; by the steady development of resistance to antibiotics so that our relatively tame staphylococcal cats have turned into ravening tigers; and by a dawning recognition of the fact that without extensive research into macromolecular structure and intracellular biochemistry and physiology no permanent advances can be made in any field of biology.

Though this edition deals mainly with the past decade there is an account of the historic experiments at Cairns, Australia, in 1943 in which their originator and designer, Neil Hamilton Fairley, laid the foundation of our knowledge of malaria prophylaxis and eradication, and furnished the strongest presumptive evidence of the existence not only of the tissue phase of malaria parasites but of the fundamental difference—in life history, danger, and treatment—between the two main kinds of malaria, Laverania malaria (the vicious visitor) and Plasmodium malaria (the lingering lodger), the descriptive phrases being the reviewer's.

In this book the whole field of tropical medicine has been thoroughly covered, recent literature has been critically examined, and at the end of each chapter an extensive list of references has been given. With the publishing world as it is to-day, it is difficult for a book to be absolutely up to date; but this one is surprisingly so. Kyasanur forest disease, endomyocardial fibrosis, and epidemic haemorrhagic fever are fully described. The deficiency diseases and the anaemias of the tropics are dealt with in an authoritative manner by Woodruff. The importance of kuru and of the haemoglobinopathies to the research worker in genetics is emphasized. Walters deals effectively with the short-term fevers, of which an ever-increasing number are being identified as due to arthropod-borne viruses—some of which exist primarily as zoonoses.

The beneficial influence of St. Pancras on recent advances is perhaps emphasized, but this is natural. The book is not a textbook and is not intended to be so, but it should be in the hands of everyone interested in tropical medicine: its possession by every candidate for a tropical diseases diploma is advisable, and for the aspirant to a tropical Membership is a "must." Doubtless it will have to be reprinted at an early date.

GEORGE R. MCROBERT.

RADIOGRAPHY IN ACUTE ABDOMINAL DISEASES

Roentgen Examinations in Acute Abdominal Diseases. By J. Frimann-Dahl, M.D., Ph.D. (Pp. 518+xiv; illustrated. £6 4s.) Oxford: Blackwell Scientific Publications. 1960.

There are few fields where close collaboration of the surgeon and the radiologist is as essential as in the diagnosis of acute abdominal diseases. The second edition of the monograph on *Roentgen Examinations in Acute Abdominal Diseases*, by Professor J. Frimann-Dahl, is a valuable contribution on this important subject, which frequently is only superficially treated in the standard textbooks of radiology.

The present edition involved some re-writing, with new chapters and illustrations. The illustrations throughout the book are of high quality, especially when one considers that this type of examination will not always permit radiographs of good quality because of the serious condition of the patient. A note on radiation hazards is included, and it is rightly pointed out that a radiographic examination of the acute abdomen is of such benefit, and so decisive for the patient's life, that the remote possibility of genetic damage must be considered a calculated risk in the patient's interest.

Though this monograph deals with investigations performed without contrast media, the use of water-soluble contrast media in abdominal emergencies, such as perforated ulcers of the stomach and duodenum, might usefully be included in future editions. The same might apply to tomography in abdominal emergencies, such as the demonstration of a ruptured kidney or other injured abdominal organs.

The importance of the book rests on the solid core of cases which have all been verified, either by clinical course, by operation, or by the findings at necropsy, and it demonstrates not only the achievements at Professor Frimann-Dahl's clinic, where the death rate

from bowel obstruction has dropped to below 5%, but how invaluable is simultaneous co-operation between the surgeon and the radiologist in acute abdominal diseases. The book should be readily available for reference in any hospital radiological or surgical library.

HENRY W. GILLESPIE.

CONTROLLING PAIN

Fundamentals of Nerve Blocking. By Vincent J. Collins, M.S., M.D. With the assistance of Emery Andrew Rovenstine, M.D. (Pp. 354; illustrated. 71s. 6d.) London: Henry Kimpton. 1960.

In effect this book represents the material presented at a course on nerve blocking held at the Bellevue Medical Centre in New York. Such courses have long enjoyed a world-wide reputation, and their success is traced to Halstead, the originator; Labat, who developed the techniques; and Rovenstine, who encouraged the clinical application of local analgesia. Dr. Collins gives these three men unstinted credit, and modestly takes none for himself. Doubtless, however, his own stature will be increased by the middle half of this book dealing with the mechanisms of pain and their control. It is a pleasure to read such a genuine and clear account of these problems, even if their solution sounds a trifle over-optimistic. These ten chapters are the real meat of the book, and fulfil a most worth-while place in the literature of local analgesia. It is no criticism to state that the surgical application of nerve blocks is ignored, for the intention is to demonstrate the therapeutic and diagnostic worth of these measures. References at the end of each chapter suggest more extensive additional reading, rather than corroborative evidence for the text.

The technical section is brief but surprisingly comprehensive. It contains nothing that is revolutionary and one could argue that there are better descriptions and illustrations elsewhere. Nevertheless, I should very much like to own this book and it can be recommended without hesitation to all who have to deal with the problem of pain and its relief.

R. BRYCE-SMITH.

WESTERN PSYCHOLOGY AND HINDU TEACHING

Western Psychotherapy and Hindu-Sâdhanâ. A Contribution to Comparative Studies in Psychology and Metaphysics. By Hans Jacobs. (Pp. 231. 35s.) London: George Allen and Unwin Ltd. 1961.

Sâdhâna means spiritual advancement, and in Hindu teaching represents a system of abstract meditation or ascetic practice evolved to achieve union with the Supreme Spirit. Human beings with their diverse inclinations and temperaments seek this objective in different ways. Acceptance of personal qualities and limitations is an essential stage in spiritual advancement. But, with discipline, release from purely personal aims can be achieved. In mundane matters reason is paramount; but reason alone is inadequate when confronted with "ultimate questions." To find the correct path, spiritual exercises (*sâdhâna*) with aspiration and passion are essential to free oneself from the external world.

Dr. Jacobs is certainly right in saying that Western psychologists and psychiatrists have much to learn from the Hindu achievements in understanding the spirit and mind of man. He would probably agree—if one might judge from his studies in Europe—that the Hindu practitioner, in his turn, can learn from his Western colleagues and particularly from Freud and Jung, whose writings are singled out as representative of Western psychology. Yet "the mere psychological viewpoint" has limitations, and pride of place is given to Indian philosophical reflection. This, it is thought, provides the guide to truth when it comes to elucidating "many issues which generally remain in the dark." A combination of the Occidental and Oriental methods has been attempted by the author; but the exposition of this procedure is not always clear. Of particular importance is a series of 30 drawings and paintings, several in colour, with explanatory notes.

Not content with examining "Western psychology" *vis-à-vis* Hindu teaching, Jacobs proceeds to a comparison of Indian and Western philosophy in general. This rather complicated extension obscures the main theme of the book. For non-Indian readers the absence of a glossary is a serious omission.

E. A. BENNET.

SURGICAL GLOVES

The Surgeon's Gloves. By Justine Randers-Pehrson, M.A. (Pp. 95+xi; illustrated. 36s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications Ltd. 1960.

The value of this little monograph lies not so much in the interesting description of the development of the surgical glove as the insight it provides into the extraordinary resistance to new ideas which, unfortunately, has so often plagued the advance of medical science.

In the case of the glove there may be some excuse, at least in the early days, when very few members of the medical profession knew what caused wound infection or realized how important it was to keep wounds clean and avoid contaminating them with dirty hands. The surgeon who changed his outdoor frock coat for a similar but blood-stained garment in the operating theatre naturally could see no point in covering his hands with gloves which, if nothing worse, reduced his sense of touch. It is interesting to note that at first gloves were used to protect the operator and not the patient, but is not that almost 50% of the present-day conception of the usefulness of surgical gloves? In the early 1800's attempts were made to find a suitable chemical protection for the hands; to-day we talk about barrier creams. No mention is made of when sterile talcum powder was first used to assist the surgeon to don his gloves, but the practice certainly existed in the earlier part of this century.

Mrs. Randers-Pehrson has given us an interesting study, compiled with great attention to detail with a large bibliography of over 200 references, and very lavishly printed. She must have burnt a lot of midnight oil, which perhaps accounts for the cost of this little book.

J. C. A. DOWSE.

BRAIN AND CORD INJURIES

Injuries of the Brain and Spinal Cord and Their Coverings. Edited by Samuel Brock. (Pp. 739+xi; illustrated. £7.) London: Cassell. 1960.

This is a well-known book the general excellence of which has been recognized for twenty years. In the revision which has taken place for this edition there are five new chapters on various aspects of the subject.

Others have been revised, often with the provision of an addendum. The new chapters on intracranial haematomas and the role of radiology in the management of head trauma deserve special mention for their outstanding clarity. Earlier editions contained a chapter on the legal aspects of trauma to the brain and spinal cord, but this has been omitted in the new volume owing to the growth of the subject, and possibly because national variations make it difficult to present a universally applicable account. Of the 31 contributors, two are from this side of the Atlantic.

On reading this edition it is clear that those chapters which have been completely revised or freshly written stand above the others. Time passes rapidly, and with the intervention of a war since the book first appeared a very large new literature on trauma has developed. Thus, it is disappointing that there are no references to work on post-traumatic epilepsy later than 1945. This excludes conclusions based on experience of head injuries in the second world war. Advances in treatment have similarly crept into addenda in some chapters, but in others may be contradicted by outdated information; for instance, "celluloid" is recommended for the repair of skull defects on page 60 and discarded for this purpose on page 249. It is to be hoped that in future editions the chapters containing addenda will be rewritten.

The index, unfortunately, is inadequate for a work which is undoubtedly used mainly for reference; such a book should err in the direction of too many cross-references and too full an index, rather than the reverse. A number of important items in the addenda have not been mentioned in the index. For instance, the subject of hypothermia is not included, "otorrhoea" and "cerebrospinal fluid" do not appear, and there are others.

However, in spite of the suggested shortcomings, this work is still one which may profitably be read from cover to cover by anyone concerned with the treatment of trauma. The emphasis laid on the sequelae of head injury has especial value. It is very well printed and produced, and should undoubtedly be obtained by medical libraries, particularly those in hospitals, to which it is confidently recommended.

PETER H. SCHURR.

ADOLESCENCE—FRENCH AND BRITISH

Adolescence. The Years of Indiscretion. By T. A. A. Hunter, T.D., M.B., M.R.C.P., and M. E. M. Herford, D.S.O., M.B.E., *M.C.*, M.D., Ch.B., D.P.H. (Pp. 160. 15s.) London: William Heinemann Medical Books Ltd. 1961.

Médecine Sociale de l'Adolescent. Sa Mise au Travail. By Louis Christiaens. Preface by Professeur Julien Marie. (Pp. 613. NF. 54.) Paris: G. Doin et Cie. 1960.

For the past year or two we have all heard adolescence spoken of as a most neglected age group, and certainly the medical problems of the adolescent have received little attention compared with that given to this group by social workers, judges, advertisers, screen moguls, T.V. producers, disc jockeys, and, in fact, nearly everyone else. Here are two books to help remedy this.

The French book, *The Social Medicine of Adolescence*, edited by Professor Louis Christiaens, provides a comprehensive guide to help doctors to understand the physical and psychological problems of young people aged between 14 and 18. The five sections of the book are: "Problems of Growth and Puberty," "Psychological Problems," "Follow-up of Defects Discovered at Routine Examinations," "The Handicapped," and "Occupational Hygiene and Social Medicine." Inevitably some of the material could well appear in a comprehensive textbook of adult medicine or of paediatrics, but the fact that so much has been gathered here between two paper covers (the volume is worthy of more permanent binding) is a great advantage to anyone who works with these young people. Inevitably, too, the balance of the book is French, with greater emphasis on the personal responsibility of the examining doctor than we should expect here, but I wish there were an English equivalent.

The English book is altogether slighter and has a different purpose. Written for a lay audience—parents, schoolteachers, youth leaders—it carries the subtitle *The Years of Indiscretion*. (The subtitle of the French book is *Introduction to Work*.) The choice of what to include reveals the long experience of the two authors. The chapters on psychological problems and the introduction to work are most helpful, but a short list of books for further reading at the end of each section would have been useful to those who need more than is here given. The book can be recommended for the audience for whom it was intended, and indeed those of us who are consulted by teenagers will gain from reading it.

D. PIRRIE.

PASTEUR

Louis Pasteur. A Master of Scientific Enquiry. By Jacques Nicolle. (Pp. 196. 35s.) London: Hutchinson. 1961.

Louis Pasteur will for ever serve as the perfect pattern of the scientific research-worker. His acuity and accuracy of observation, intuitive choice of experiment, refusal to entertain theories until all the ascertainable facts were before him, and balanced judgment have seldom been equalled and never surpassed. Add to this his infinite patience and remarkable faculty for applying the results of his researches for the benefit of the community, and the outside observer can but marvel. This book by Jacques Nicolle is not a rival to but supplements Vallery-Radot's well-known work. In the ten carefully written chapters the author succinctly describes the working out of the ten major scientific problems which Pasteur solved, starting with the crystallography of the tartaric acids and ending with the successful immunization against rabies. Some material which might have hindered the telling of the story is included in two appendices; and there is a useful annotated list of names.

Here is a story which should interest everybody and should be an inspiration to every young research student in chemistry, biology, and medicine. In fact, the virtues which Pasteur possessed and exercised are universally applicable in research work of every kind.

ZACHARY COPE.

NERVE ENDINGS IN SKIN

Nerve Endings in Normal and Pathologic Skin. Contributions to the Anatomy of Sensation. By R. K. Winkelmann, M.D., Ph.D. (Pp. 195+viii; illustrated. 60s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications Ltd. 1960.

This is a concise and complete account of the nerve endings in the skin, which may pave the way to a better understanding of function and sensation. It is a difficult field, to which Dr. Winkelmann has made numerous important contributions in the past ten years, and dermatologists, anatomists, and physiologists will appreciate the presentation of this work as a whole, particularly as the author is mindful of the clinical applications.

The historical and the technical aspects are dealt with faithfully: the literature is reviewed—there are more than 400 references—and the findings and hypotheses put forward by leading authorities are helpfully presented. Dr. Winkelmann indicates, from his own researches, where he is in agreement or where he has reason to differ from current views. He subscribes and pays tribute to the fundamental work of Weddell in Great Britain, particularly in regard to the reception of patterns by the nerve network in the skin in relation to our perception of sensation, as opposed to the conception of specific function attributable to special end-organs. He suggests that, since itching can be produced by chemical means, it is possible that other mild sensory responses are on a chemical basis.

Dr. Winkelmann emphasizes the function of the hair follicle as a sense organ, which is replaced by the muco-cutaneous or "genital" end-organs in the neighbourhood of orifices. The black and white illustrations of these anatomical features are of excellent quality. There are useful chapters on the innervation of different skin areas and structures and on the effects of damage or disease of nerves within and outside the skin. There is no convincing evidence of anatomical changes in nerves in association with skin reactions such as eczema, alopecia, and pemphigus. This is a most important and informative work of reference on a difficult subject. It is attractively presented in this slim volume.

J. T. INGRAM.

HOSPITAL ALMONERS

The Story of Hospital Almoners. The Birth of a Profession. By E. Moberly Bell, with a foreword by Sir Ernest Rock Carling, F.R.C.S., F.R.C.P. (Pp. 160; illustrated. 13s. 6d.) London: Faber and Faber. 1961.

The sub-title of this book, *The Birth of a Profession*, is apt. The work of hospital almoners in the modern sense began at the turn of the century mainly as an effort to reduce congestion in out-patients departments and to check abuse of the services the hospitals offered. The midwife was Charles Lock, the General Secretary of the Charity Organization Society. He was interested in the "reform of the medical charities," and was largely responsible for the pioneer appointment of a lady almoner at the Royal Free Hospital in 1895. A similar appointment was made at the Westminster Hospital in 1899, and by 1903 seven almoners were at work in London hospitals. It was not, however, until 1905 that Anne Cummins was appointed to St. Thomas's Hospital, and much of the book is a biography of this talented lady. In 1909 the Cicely Northcote Trust was set up at St. Thomas's Hospital "to study the social causes of ill health." The endowment came from a grateful patient who had visited the Massachusetts General Hospital, where a social worker had been appointed in 1905.

The hospital almoner's work has long grown away from the idea that it is primarily for the purpose of assessing what incomes prospective patients have and refusing free treatment to those who can afford to pay for it privately. "The almoner's work is an assessment of the patient's needs rather than of the patient's means."

It is a well-written and well-indexed little book which will be read with interest by all concerned with the social aspects of illness.

ALLEN DALEY.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

Thrombosis and Anticoagulant Therapy. Proceedings of a Symposium arranged by Professor P. A. Owren, Professor R. B. Hunter, and Dr. W. Walker, and held in Queen's College, Dundee, on 29 and 30 September, and 1 October, 1960. Edited by W. Walker. (Pp. 106; illustrated. No price.) Dundee: D. C. Thomson and Co. Ltd. Edinburgh and London: E. and S. Livingstone. 1961.

The Transactions of the Hunterian Society, 1959-60. Honorary Editors: E. F. Stewart and Gordon Sears. (Pp. 151. No price.) London: The Metropolis Press. 1961.

Advances in Blood Grouping. By Alexander S. Wiener, M.D., F.A.C.P. (Pp. 549+xii; illustrated. $11.) New York and London: Grune and Stratton. 1961.

Augenheilkunde. Ein Lehrbuch für Studium und Praxis. By F. Rintelen. (Pp. 455+xxvii; illustrated. Sw.Fr. 65.) Basle, New York: S. Karger Verlag. 1961.

The Transactions of the Second Conference on the Health of Executives held in the Royal Festival Hall, London, 24th November 1960. (Pp. 112. 15s.) London: The Chest and Heart Association, Tavistock House North, London, W.C.1.

Carcinoma of the Colon. By Edward G. Muir, M.S., F.R.C.S. (Pp. 181+vii; illustrated. 42s.) London: Edward Arnold (Publishers) Ltd. 1961.

X-Rays. Their Origin, Dosage, and Practical Application. By W. E. Schall, B.Sc., F.Inst.P., Hon.F.S.R. Eighth edition. (Pp. 348+xi; illustrated. 50s.) Bristol: John Wright and Sons Ltd. 1961.

Arteriosklerose. Ätiologie, Pathologie, Klinik und Therapie. Edited by Professor Dr. Gotthard Schettler. (Pp. 728+xvi; illustrated. DM. 98.) Stuttgart: Georg Thieme Verlag. 1961.

The Psychological Care of the Child in Hospital. By Agatha H. Bowley, Ph.D., F.B.Psy.S. (Pp. 47; illustrated. 4s. 6d.) Edinburgh and London: E. and S. Livingstone, Ltd. 1961.

Neuroradiology Workshop. Volume 1: Scalp, Skull and Meninges. By Leo M. Davidoff, M.D., Harold G. Jacobson, M.D., and Harry M. Zimmerman, M.D. (Pp. 256+vii; illustrated. $16.50.) New York and London: Grune and Stratton. 1961.

Synovial Joints. Their Structure and Mechanics. By C. H. Barnett, M.A., M.B., F.R.C.S., D. V. Davies, M.A., M.B., B.S., and M. A MacConaill, M.B., D.Sc., M.R.I.A. (Pp. 304+xi; illustrated. 50s.) London: Longmans. 1961.

Britain's Search for Health. The First Decade of the National Health Service. By Paul F. Gemmill. (Pp. 171. 32s.) Philadelphia: University of Pennsylvania Press. 1961.

Cardiopericardiomyopexy. New Surgical Treatment for Heart Diseases. By Dr. Aaron N. Gorelik in collaboration with Professor Camille Lian, Professor Louis Thieblot, Dr. Mendel Jacobi, Dr. Ralph Ricciardi, and Dr. Madeleine Hascher. (Pp. 176+xiv; illustrated. No price.) New York: Myopexy Association Inc. 1961.

Conquering Your Allergy. By Boen Swinny, M.D. Introduction by C. J. C. Britton, M.D., Ch.B., D.P.H. (Pp. 127. 12s. 6d.) London: Hammond, Hammond and Company. 1961.

La Radiculographie Lombo-Sacrée par Substance Iodée Hydrosoluble et Resorbable. By Jacques Ferrand, Jean Robert D'Eshougues, Jacques Barsotti. (Pp. 108; illustrated. Paris: L'Expansion Scientifique Française. 1961.

Primer Congreso Peruano de Neuro-Psiquiatria. 3 al 7 de Noviembre de 1958, Lima-Peru. (Pp. 197-508; illustrated. No price.) 1961.

The Day Hospital Movement in Great Britain. By James Farndale, B.Com., F.H.A., M.R.S.H. (Pp. 430; illustrated. 84s.) London: Pergamon Press. 1961.

The Person Symbol in Clinical Medicine. By Robert Cohn, M.D. (Pp. 196; illustrated. 80s.) Springfield, Illinois: Charles C. Thomas. 1961.

Les Ictères Postopératoires Précoces. By F. Poilleux and A. Kapandji. (Pp. 107; illustrated. NF. 14.) Paris: L'Expansion Scientific Française. 1961.

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N.H.S. IN FUZZILAND

Profession, politician, and public are in the National Health Service in a triangular relationship which, in the words of the Minister of Health, Mr. J. Enoch Powell, may be "inherently unstable." In his address at Winchester last week (published in the *Journal* of May 27) he used the words "inherently unstable" in relation to breach of contract leading to the imposition of a fine upon a doctor as a consequence. It was this part of his speech which provoked most comment in the press, which without exception clamoured for the publication of such a doctor's name. The Minister will undoubtedly continue to be harried to depart from his present conclusion that "the administrator ought to hold firm against any action or any attitudes, however tempting, which would turn him into an instrument of professional discipline, of civil redress, or of criminal sanction."

The strongest protection the public has is the medical profession's jealous concern for its own reputation. The doctor guilty of "infamous conduct in a professional respect" will find himself summoned before the General Medical Council, with its power to remove his name from the *Medical Register*. Any patient believing that a doctor has been negligent in treatment can bring an action against him in the courts, and if found guilty the doctor will not only suffer the legal penalty but may also subsequently have his name removed from the *Register*. The enormous increase in litigation during the past 10 years or so shows that the public is well enough aware of its rights at law. The aggrieved patient or his relatives can also lodge a complaint with the local executive council against a general practitioner, and if he is found to have broken his contract the executive council can by way of penalty recommend that part of his remuneration be withheld.

The press clamours for the publication of such a doctor's name. The whole matter is bedevilled by the curious position in which the three parties are placed. As Mr. Powell points out, the contract is between the doctor and the Minister's agent "for the performance of services not by one to the other but by one to a third party"—namely, the patient. Leaving aside the complexities of the relationship, we should ask the question whether it would be in the interests of the public that doctors who have been fined should have their names published in the newspapers. Any human institution must have its own methods of dealing with internal breaches of discipline, just as any household has. When these breaches are not such as to demand redress in a court of law, they can fittingly be described as domestic. Charges of a breach of domestic discipline are apt to arise in an institution such as the N.H.S., and they are best dealt with domestically. The doctor who has been fined partly at the instance of his colleagues for a lapse from what they expect of him has had his lesson. The publication of his name can do only harm to those two or three thousand other of his patients for whose professional care he is responsible. In other words, a domestic lapse in one instance should not be allowed to impair the doctor–patient relationship existing between him and the community he looks after. The public as patient should think a bit more deeply about this, knowing as they do that the G.M.C. and the courts are there to protect them against infamous conduct and grave negligence.

The publicity given to this aspect of Mr. Powell's masterly address has deprived newspaper readers of learning something about his close analysis of the relationship between politician and profession in the National Health Service. He begins by pointing out something which seems to have been overlooked by some of his predecessors—namely, that the responsibility of the Minister of Health is not "the prevention, diagnosis, and treatment of illness" but the establishment of a comprehensive health service to secure these things. Though the division of function is clear cut, it is, to use Mr. Powell's words, "too austere to exist as a practical reality." In an exploration of what he calls this "fuzziland" he admits that the public will not acquit him from the responsibility of taking decisions that affect clinical matters. And to this he adds the cogent rider that it is important that there should always be "a substantial amount both of research and of treatment which is not financed by the State and for which the Minister is not responsible . . ."

The N.H.S. has introduced a large number of artificial factors into the life of a free profession. Freedom to discipline itself, to determine its own education, to formulate its own ethical code, to decide within limits its own remuneration, is in fact part and parcel of what we call a profession. To the extent to which these freedoms are restricted, to that extent will the term "profession" lose much of its meaning.

The introduction of the N.H.S. has been accompanied by what Mr. Powell calls an "artificial mechanism" for determining the amount and system of payment and for regulating the entry of trainees for medicine. The acceptance of the Pilkington recommendations and the establishment of the Review Body, he points out, "have veiled . . . the essentially artificial nature of the resultant figures. . . ." Still another *artificial* element to which he draws attention is "distinction awards," a device he regards as "inherently imperfect" but bound up with "status."

In a vast enterprise like the N.H.S., administered by the State, conflict between the profession and the politician is inevitable. Nor, for that matter, is conflict undesirable, because in its absence complacency and apathy will work to the detriment of both. Such conflict can at least be made more constructive if politician and profession understand their different approaches and reactions to a common problem. Mr. Powell's analysis in this respect is illuminating and should serve to clear away a good deal of natural misunderstanding. The doctor, in whatever branch of medicine he practises, is concerned with the individual; the politician, to use Mr. Powell's words, "is all the time concerned with the general consequences of individual decisions." In a memorable sentence he writes: "One might say that for the doctor the general law is only relevant so far as it helps the individual, while for the politician the individual case is only relevant so far as it illuminates the general law": the paradox is that in this statement he makes out the politician to be more of a scientist than the medical man. For the public the N.H.S. is Wonderland; for the Minister of Health it appears to be Fuzziland; for the medical profession it looks at times to be No Man's Land. But Mr. Powell's cogent analysis in his Winchester Address should be a great help for those who are trying to promote the evolution of the N.H.S. into something much better than it is at present.

NORMAL AND LEUKAEMIC HAEMOPOIESIS

Three years ago C. E. Ford and his colleagues,[1] following up the clue provided by observations on leukaemic mice,[2] observed changes in the chromosomes in one human case of acute leukaemia. The cytological abnormality was detected in a culture of bone-marrow. In the *Journal* this week (p. 1564) Dr. A. G. Baikie and his colleagues have reviewed their observations on a series of 31 cases, from 22 of which satisfactory preparations were available. Not all cases of leukaemia provide myeloid material suitable for analysis, though a notable technical advance has been the discovery that cells which can be induced to undergo mitotic division are obtainable from the peripheral blood of both normal and leukaemic subjects.[3] Thus Baikie and colleagues examined preparations from both peripheral blood and marrow. As a rule, it can be said that the two sources give the same qualitative picture.

At present, interpretation of the cells seen in the peripheral blood is still somewhat obscure. The presence of "blast" cells in the circulating blood has long been one of the criteria of diagnosis of leukaemia. They have been recognized from finding atypical cells which on morphological grounds are called myeloblasts, lymphoblasts, primitive monocytes, or stem cells. It is rare to find one spontaneously in mitosis. Now, however, it is recognized that even in normal subjects some of the typical circulating leucocytes with the appearance of monocytes or large lymphocytes are primitive in the sense that they are actively synthesizing D.N.A.[4] These presumably are the cells which can be induced in culture to divide and show their normal set of chromosomes to contrast with the leukaemic cells, which may have chromosomes abnormal in number, form, or both.

The old concept was that the leukaemic cells were a spill-over or metastasis from the malignant myeloid tissue. Are the cells which are normally synthesizing D.N.A. a similar and physiological metastasis? And if so what is their function? J. F. Loutit,[5] taking as a model certain biochemical cycles (like the Krebs cycle), postulated that a similar cellular cycle occurs in haemopoiesis. In the marrow multipotent stem cells provide a lymphopoietic line of cells as well as the conventional erythropoietic and granulopoietic lines—this is the standard monophyletic hypothesis. The primitive lymphoid cells are carried by the bloodstream to lymph tissue, where they mature, re-enter the blood, and ultimately reach the marrow to expire and return D.N.A. or other essential material to the factory. This hypothesis was based on experiments with mice in which the myeloid and lymphoid tissues were made aplastic with *x* rays and then restored with intravascular injections of active myeloid tissue from a donor.

[1] Ford, C. E., Jacobs, P. A., and Lajtha, L. G., *Nature (Lond.)*, 1958, **181**, 1565.
[2] —— Hamerton, J. L., and Mole, R. H., *J. cell. comp. Physiol.*, 1958, **52**, Suppl. 1, 235.
[3] Nowell, P. C., and Hungerford, D. A., *J. Nat. Cancer Inst.*, 1960, **25**, 85.
[4] Bond, V. P., Cronkite, E. P., Fliedner, T. N., and Schork, P. K., *Science*, 1958, **128**, 202.
[5] Loutit, J. F., *Ann. N.Y. Acad. Sci.*, 1960, **88**, 122.
[6] Popp, R. A., *Proc. Soc. exp. Biol. (N.Y.)*, 1960, **104**, 722.
[7] Lajtha, L. G., and Oliver, R., *Ciba Foundation Symposium on Haemopoiesis*, p. 289. London, 1960.
[8] Barnes, D. W. H., Ford, C. E., and Loutit, J. F., *Surg.*, 1959, **30**, 762.
[9] Tough, I. M., *et al.*, *Lancet*, 1961, **1**, 411.

But it is now seen to be incomplete, for R. A. Popp[6] has shown that a sufficiently large dose of leucocytes from normal peripheral blood will also restore erythropoiesis. Presumably, therefore, the primitive D.N.A.-synthesizing cells in the peripheral blood are not limited to lymphopoietic cells but include erythropoietic and granulopoietic (or stem) cells also. This accords with the fact that their morphology has been reported as mixed—monocytic or large lymphocytic.

While an export of lymphopoietic cells from the marrow is explicable as a sole or supplementary means of producing lymphocytes, what is the explanation of an export of myeloid cells? Or is it an import of primitive stem cells from some dispersed mesoblastic tissue supplementing the marrow? On the model of L. G. Lajtha and R. Oliver,[7] limited by them to the erythron but applicable to other myeloid cell lines, such supplementation would seem unnecessary. Moreover, D. W. H. Barnes and colleagues[8] have shown with irradiated mice that a total of a few million myeloid cells (presumably containing only a few tens of thousands of stem cells) on serial passage is for some years the sole source of the myeloid and lymphoid tissue. The weight of evidence therefore suggests that the normal primitive cells are an export from the marrow, and the same seems to apply in leukaemia. In the cases discussed by Baikie and colleagues, though atypical cells were found in the circulation, tissue-cultures of skin, presumably of primitive mesoblastic cells, showed normal chromosomal patterns.

It seems therefore that the extrusion of primitive cells from the site of production into the peripheral blood is not a specific phenomenon of leukaemia. Indeed, it is well known that many leukaemias are aleukaemic. The characteristic of the disease lies in the production of abnormal cells. How the relatively constant chromosomal abnormality in chronic myeloid leukaemia[9] and the variable abnormality seen with the light microscope in acute leukaemia are related to the fundamental causes still remains to be elucidated.

RISKS OF HYPERVENTILATION BEFORE SWIMMING UNDER WATER

Professional swimming coaches have long known that sudden loss of consciousness is not uncommon while training for "plunge" competitions, in which it is standard practice to hyperventilate for a minute or two before diving, in order to increase performance. A. B. Craig[1] now reports on eight patients who lost consciousness but survived while swimming under water and five others who drowned under similar circumstances. Unfortunately no measurements under experimental conditions were made, and it is well known that clinical speculations on mechanisms causing the loss of consciousness usually turn out to be incorrect. Craig believes that hypoxia is the cause, and that may be the explanation of those cases in which the bather lost consciousness only after swimming several lengths of the bath. But "plungers" and some under-water swimmers can lose consciousness very soon after immersion. It is almost certain that the mechanism here is the performance of a Valsalva manœuvre directly after hyperventilation. It is interesting that in all Craig's cases the swimmer hyperventilated violently before going in.

Hyperventilation, by lowering pCO_2, causes constriction of cerebral vessels and dilatation of muscle vessels. On subsequently performing the Valsalva manœuvre loss of consciousness is startlingly sudden,[2] and in these conditions it is incorrect to assume[3] that there are 5 seconds' warning before syncope. The Valsalva manœuvre is carried out by straining against a blocked airway, thus raising the intrathoracic pressure. It occurs in everyday life on defaecation, playing wind instruments, coughing, and in many forms of muscular exertion. By trapping blood in the peripheral veins, cardiac filling pressure and stroke output can fall to low levels. The tense streamlined attitude of the "plunger" and the exertions of the under-water swimmer provide suitable conditions for this. It is possible that the Valsalva manœuvre is still the mechanism causing loss of consciousness when fairly long distances have been swum. For at extremes of muscular exertion there is a strong tendency to raise the intrathoracic pressure to high levels, as in lifting heavy weights or struggling in a tightly packed crowd. Perhaps more than one mechanism is operating. But experimental data are now required rather than speculations. Continuous intrathoracic and intra-arterial records of volunteers swimming under water in a tank should not be impossible to obtain, though samples for measuring arterial pO_2 and pCO_2 present something of a problem.

In practice Craig is right to stress the dangers of previous hyperventilation, and unfortunately it is the young, supremely fit individual whose circulation is most likely to respond in this way. There is a strong case for warning schoolmasters, swimming teachers, and life-guards that there are risks attached to this common practice. This sort of problem raises the question of how far it is possible to persuade the general public to look after their own and other people's safety. Stout business-men in fast cars continue to cough their way to work. Only a few doctors, a notoriously hypochondriacal profession, seem to have given up smoking. Many people leave a year's sedentary life to break their legs on alpine snows in winter. Some may claim that loss of consciousness under water is a remote chance of a healthy sport, but the tragedy of a dead child retrieved from bath or sea is one few of us care to contemplate.

[1] Craig, A. B., *J. Amer. med. Ass.*, 1961, **176**, 255.
[2] Howard, P., Leathart, G. L., Dornhorst, A. C., and Sharpey-Schafer, E. P., *Brit. med. J.*, 1951, **2**, 382.
[3] Engel, G. L., *Fainting*, 1950, Springfield.

ADDER BITES

Our only poisonous snake is a shy, mostly nocturnal animal which bites only when disturbed. So the diagnosis of adder bite is usually made on the story of sharp pain and the finding of two puncture marks about 1 cm. apart. Swelling and discoloration may appear within minutes. An alleged snake bite in Ireland, the Isle of Man, or the Channel Islands is probably a sting by an unnoticed insect, as snakes are unknown in these parts. If a patient says he saw the snake thrashing about he has probably only been frightened by a harmless grass snake, for an adder about to strike remains motionless until the victim is within range. Fatal cases are rare, but the 400 requests a year for antivenin indicate that bites are fairly common.[1] A full account of a severe but non-fatal case is published in the *Journal* this week (p. 1587) by Drs. G. C. Arneil and J. C. Maclaurin.

Most adder bites in adults are not serious; sometimes no signs or symptoms of poisoning follow. The amount of poison injected is variable, and this is partly responsible for the wide variation in the effects that is a well-known feature of snake bites. Suction of the bite sounds reasonable (if the lips are not cracked) and natural, but even if done at once it is very doubtful if it is of any more than psychological value. Experimental evidence is against it.[2] A tourniquet such as a handkerchief, *if applied at once by a doctor*, may be of some value, and as the poison travels by superficial lymphatics it should not be tight. But it is best avoided by a lay person, who might apply it with excessive zeal. "Slash and suck" measures are frowned upon.

The victim is often very frightened, and the best first-aid is to reassure him, to immobilize the bitten place, and to get him to a doctor. It should soon be clear whether the bite is serious or not. The recent case, reported in the newspapers, of the death of a 12-year-old girl after immediate, severe collapse may have been caused by the venom entering a small vein. When the symptoms are more than trivial, Pasteur Institute antivenin should be given. A list of hospitals where this is kept available under the aegis of the Ministry of Health is given in our "Any Questions?" section this week (p. 1621), but there appear to be no great difficulties about storing antivenin, and regional hospital boards might consider whether enough hospitals in their regions keep supplies, especially hospitals near heaths where both adders and picnickers abound.

Serum must be given cautiously; one death in 1957 was attributed to it and not to the poison. Small people require a large dose. It is best to start with an intramuscular injection of 0.2 ml. in all cases and to wait 20 minutes or more before giving the full dose of 10 to 20 ml. either intramuscularly with 1,500 units of hyaluronidase or intravenously. In all cases it is wise to give an antihistamine drug too. In a patient known to suffer from asthma or eczema who must be given a serum a series of graduated doses is indicated. T. C. Morton[3] advocates the local injection of a little serum down the fang punctures. Antivenin given by the isolation-perfusion technique is as yet experimental.[4] Administration of cortisone or A.C.T.H. is advisable in severe cases.[5] Adrenaline injection *B.P.* (1 in 1,000), aminophylline *B.P.* (0.25 g. in 10 ml.), and an antihistamine such as chlorpheniramine (10 mg. in 1 ml.) should always be at hand for injection. Tetanus antitoxin 3,000 units should be given unless the patient is known to have been actively immunized by toxoid. As toxin might interfere with grouping and cross-matching, this procedure should be done early in case transfusion is needed.

[1] Birch, C. A., *Practitioner*, 1959, **183**, 105.
[2] Leopold, R. S., and Huber, G. S., *U.S. armed Forces med. J.*, 1960, **11**, 682.
[3] Morton, T. C., *Brit. med. J.*, 1960, **2**, 372.
[4] Borden, J., Fonkalsrud, E. W., Newcomer, V. D., Rochlin, D. B., and Longmire, W. P., *Surgery*, 1961, **49**, 303.
[5] Ariff, A. W., *Brit. med. J.*, 1955, **2**, 205.

SHORTAGE OF DIETITIANS

Dietitians are necessary members of the staff of general hospitals if patients are to benefit from current knowledge of nutrition in health and disease. Their duties include drawing up therapeutic diets for dyspeptic, diabetic, oedematous, and obese patients, supervision of dietary restriction during some diagnostic tests, giving of advice to pregnant women and mothers of young children on correct feeding methods, and helping the elderly to plan and budget for their meals. They are able to instruct nurses and medical students on the principles of nutrition and to advise catering officers on the content of hospital menus. Unfortunately only a minority of hospitals are able to provide skilled dietetic services for their patients because the number of dietitians now working and training in hospitals is woefully inadequate. Authoritative estimates of the numbers necessary in British hospitals based either on numbers of beds or on the population of patients likely to need dietary treatment have varied between 500[1] and 1,500,[2] while more recently a figure of 700 has been suggested.[3] Since in 1959 only 279 full- or part-time dietitians were reported to be working in hospitals in England and Wales,[4] it will be seen that their numbers should be trebled if a full dietetic service is to be provided. Despite vigorous efforts by the British Dietetic Association to improve recruitment, only 40 students begin their training each year.[4] The scarcity of dietitians in non-teaching and in provincial hospitals is shown by the fact that 54% of all hospital dietitians work in teaching hospitals and many of the rest are employed by the four metropolitan regional hospital boards.

Because of this unsatisfactory state of affairs the Catering and Diet Committee of King Edward's Hospital Fund, under the chairmanship of Dr. F. Avery Jones, began in 1957 to inquire into the present position of diet therapy in hospitals, the work done by dietitians within the hospital service, and the reasons for, and effects of, the acute shortage of dietitians throughout the country.[5] The committee found that young people

[1] *Reports of the Committees on Medical Auxiliaries*, 1951. H.M.S.O., London.
[2] Memorandum of the Planning Committee of the Nutrition Society (English Group), 1945.
[3] *Memorandum on the Shortage of Dietitians*, 1960. King Edward's Hospital Fund for London.
[4] Report of the Fact Finding Committee of the British Dietetic Association, *Nutrition*, 1960, **14**, No. 2.

leaving school were not attracted to dietetics as a profession, for it requires a high academic standard on entry and a long and expensive course, after which the financial rewards and conditions of service in hospitals are comparatively poor. Matters are worsened by the often lukewarm support and interest from medical, nursing, and catering staffs and by the poor kitchen and office accommodation provided in many hospitals. Catering and other industries, by offering more attractive and lucrative posts, tempt many dietitians from the hospital service.

Recommendations made by Dr. Avery Jones's committee for improving conditions and recruitment include a shortening and replanning of the training course to a three-year period, which should be followed by a compulsory year's internship in a hospital dietetic department immediately preceding registration. The standard of a nationally accepted certificate or diploma should be supervised by the British Dietetic Association and State registration of all dietitians enforced. Recruitment would be encouraged if working conditions, professional status, accommodation in hospital, and salary scales were all improved, and if more frequent and liberal financial grants were made to students in training. The Catering and Diet Committee of the King's Fund concludes that a combined effort by the British Dietetic Association, the medical profession, and the Ministry of Health will be needed to overcome the present acute shortage of dietitians.

PROBLEMS OF JOINT MOVEMENT

Though the mechanical functions of a joint seem to be obvious, we are in fact rather ignorant about the biophysical principles at work. A widely held theory of joint lubrication, postulated by M. A. MacConaill,[1] is that it takes place by so-called hydrodynamic or full-film lubrication. On this theory fluid pressure is thought to be generated by a wedge of lubricant formed by the motion of the surfaces: this pressure supports the load and keeps the sliding surfaces separated on a cushion of lubricant. The nature of the substances forming the opposing surfaces and the nature of the lubricant (apart from its viscosity) are unimportant. J. Charnley,[2] however, points out objections to this concept of joint movement. Hydrodynamic lubrication is not suited to reciprocal motion, as occurs in a joint, because the fluid wedge developed for motion in one direction is immediately destroyed as motion takes place in the opposite direction; nor is hydrodynamic lubrication easily achieved with slow-moving surfaces under heavy loads. In contrast, a second type of lubrication, boundary lubrication, depends on the quality of the sliding surfaces and that of the lubricating fluid, since the lubricant here has an affinity for the surface, and motion takes place between monomolecular films of lubricant chemically adherent to the underlying surface. This type of lubrication is better suited to slow reciprocating movement under heavy loads, and might therefore be expected on theoretical grounds to occur in joints.

With boundary lubrication the coefficient of friction is constant for all speeds of movement, whereas with hydrodynamic lubrication it diminishes with decreasing speed. Using a human ankle-joint from a cadaver as the bearing of a pendulum, Charnley found that the frictional resistance was the same at all speeds of sliding of the cartilage surfaces; this supports the idea that the predominant mechanism in joint lubrication is a boundary phenomenon. The coefficient of friction in these studies (as in the earlier experiments of E. S. Jones[3]) was found to be remarkably low—about 0.01, or one-third of that for ice sliding on ice.

V. Wright and R. J. Johns[4] have examined joint stiffness in living subjects, using a heavy pendulum to impose a rotary motion on the second metacarpophalangeal joint. By measuring the torque required to impose the motion, the amplitude of rotation, and the rotational velocity, they have analysed various factors in joint stiffness and conclude that, both in normal and arthritic joints, the major components are elasticity and plasticity. Viscous stiffness is much less important and inertial stiffness is negligible, as is frictional stiffness, even in badly damaged joints.

Morning stiffness, a common symptom in rheumatoid arthritis, has been objectively demonstrated in the metacarpophalangeal joint by J. T. Scott,[5] using an extension spring. Morning stiffness is accompanied by an increase in the volume of the hand, which suggests that it is due to oedema. But normal subjects without morning stiffness are also found to have a greater volume of the hand in the morning than in the evening, probably owing partly to immobility during sleep and partly to diminished nocturnal excretion of water and electrolytes. This variation is sometimes, but not always, greater in rheumatoid than in normal subjects, and Scott suggests that, while an increased volume of the hand is a contributing factor in morning stiffness, there is probably a further underlying mechanism, such as a diurnal variation in the elasticity of connective tissue.

PROTEIN REQUIREMENTS IN EARLY LIFE

For the nutrition of the infant and young child an adequate intake of good protein, providing all the amino-acids necessary for the formation of new tissues, is a first requisite. The important questions of the amounts and the quality of the protein required at different ages have recently been admirably reviewed by five American paediatricians—L. E. Holt and colleagues.[1] Protein, they point out, is necessary not only for increasing the bulk of the tissues, but also for their maturation. Thus the body of an infant born at full term contains only 2% of nitrogen, as compared

[1] MacConaill, M. A., *J. Anat. (Lond.)*, 1932, **66**, 210.
[2] Charnley, J., *Ann. rheum. Dis.*, 1960, **19**, 10.
[3] Jones, E. S., *Lancet* 1934, **1**, 1426.
[4] Wright, V., and Johns, R. J., *Bull. Johns Hopk. Hosp.*, 1960, **106**, 215.
[5] Scott, J. T., *Ann. rheum. Dis.*, 1960, **19**, 361.

with 2.8% at 9 months and a maximum of 3.0% at 4 years. This double demand for protein, to allow both rapid growth and increase in protein concentration, means that, in comparison with body weight, an infant needs about five times as much protein as an adult. At birth an intake of 2.0 g. of protein per kg. of body weight is needed, as compared with only 0.35–0.45 g. in the adult. In premature infants the demand for protein is even greater. Experiments have shown that the maturation of the tissues may be accelerated by an abnormally high intake of protein, but whether this acceleration confers any clinical benefit is doubtful. In later childhood protein requirements are somewhat increased at puberty, with a maximum for girls at the ages of 11–13 years, and for boys at 14–16 years.

Protein deficiency in infants causes the condition known as kwashiorkor, with lesions which vary according to whether the diet is also deficient in calories and other nutrients. Usually the abnormalities include apathy, wasting or oedema, scaling of the skin and depigmentation of the hair, enlargement of the liver, and anaemia. Kwashiorkor is common in many under-developed parts of the world, particularly in Africa, but is almost unknown in better-off countries. Subacute deficiency of protein, however, may possibly occur among generally well-fed communities as a secondary effect of disease or other forms of stress. There is no evidence that the provision of a diet rich in protein allows the body to lay down stores of protein to meet future emergencies, in the same way as stores of fat and glycogen are accumulated. Protein is held in the body only as a structural part of the cells. The possibility of stores of "labile nitrogen," in forms other than protein, requires further study.

Further research is also required on the effect of imbalance of amino-acids on the requirement for each individual amino-acid. Requirements can be satisfied most economically when the amino-acids are supplied as an "ideal" protein, to which the proteins of human and cows' milk and egg-white closely approach in composition. Experiments have shown that unnecessarily large intakes of one amino-acid can affect the requirements of others. Thus overdosing of human subjects with leucine will decrease the levels of valine, tyrosine, isoleucine, serine, and phenyl-alanine in the blood plasma. Another problem is to elucidate the relationship between the adequacy of the protein intake and resistance to disease. The general idea that a malnourished subject is less resistant than a well-nourished subject is questionable. The influence on resistance appears to depend on whether the host or the parasite is the more vulnerable to protein deficiency. Usually the requirements of bacteria for protein are less urgent than those of the host, and hence the host benefits more than his parasites from a good supply of protein. Viruses, however, are even more avid for protein than is their host, and thrive best in well-nourished subjects. Helminths are stated to resemble bacteria in doing better in a host whose intake of protein is low, but possibly the host-parasite relationship may vary according to the stage of the parasite's life cycle. Many other aspects of protein metabolism and requirements are discussed in this excellent review. It is no criticism to say that it raises many more questions than it is able to answer.

[1] Holt, L. E., Syorgy, P., Pratt, E. L., Snyderman, S. E., and Wallace, W. M., *Protein and Amino-acid Requirements in Early Life*, 1960, New York University Press.

MEDICAL OFFICERS IN THE ARMED FORCES

A meeting of the Armed Forces Committee of the British Medical Association has been called for June 12 in order to discuss the whole question of the pay of medical officers, both regular and National Service. The financial value which the Ministry of Defence puts on the work of the National Service medical officers is ludicrously inadequate and has provoked indignant protests.[1] Unfortunately the Ministry's niggardliness not only affects individuals but is likely to make it even more difficult for the Services to find the medical officers they will be needing when they are entirely dependent on voluntary recruitment. Already recruitment to the R.A.M.C. has fallen far behind requirements, and there is evidence that the Royal Navy and the Royal Air Force are facing the same difficulty.

It might have been expected, therefore, that the recently announced increases in pay[2] for medical officers in the armed Forces would have offered some encouragement to young doctors thinking of taking a regular commission and to the older officers who have already served for many years. But the additional 3s. per day for junior medical officers and 2s. per day for senior officers (majors and above in the R.A.M.C., or equivalent ranks in other Services), excluding National Service officers, represents nothing more than a trifling increment. The pay of a lieutenant in the R.A.M.C. has been raised by the new increases from £730 to £785 per annum. In relation to the increases offered to doctors in the N.H.S. as a result of the Pilkington Report, this recent rise for medical officers in the Forces is ridiculously small. It is true that the gratuities offered to new entrants on short-service commissions have been substantially increased—£1,500 for three years' service and £3,000 for five years—but the medical services of the Forces cannot be satisfactorily manned by officers on short-service commissions.

The Ministry of Defence, by its recent decisions and actions, is discouraging recruitment of medical officers to the Forces. The B.M.A., through its Armed Forces Committee, is, as the Ministry well knows, eager and willing to help the Ministry to overcome the very real difficulties of the present dangerous situation. But the relationship between the B.M.A. and the Ministry is hardly likely to be improved by the Ministry's action in announcing to the press the recent salary increases for medical officers before communicating them to the Association.

[1] *Brit. med. J.*, April 22, 1961, p. 1161.
[2] *Supplement*, May 27, 1961, p. 266.

EVOLUTION IN THE MENTAL HOSPITAL

REVIEW OF A HOSPITAL POPULATION

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A large proportion of all patients under care in mental hospitals show no serious disturbance of behaviour, and their retention is determined largely by social factors. Cross *et al.* (1957) surveyed the chronic population of a large mental hospital, and found that most of the patients had been under care continuously for 10 years or more; only a very small proportion required constant vigilance, while about two-thirds needed only "routine care." The degree of supervision accorded seemed to depend as much on ward tradition and administrative policy as on the patients' mental disturbance. Nearly one-half of the patients were totally unemployed, and many of the remainder had only spasmodic or nominal employment. The investigators concluded that there was a need for imaginative schemes of occupation and rehabilitation, and that all intermediate stages of care should be tried, between the mental hospital on the one hand and normal family life on the other.

Garratt *et al.* (1958), from a study of the four Birmingham mental hospitals, found that of a large number of patients reviewed 75% needed only limited hospital facilities, while 12% needed no hospital facilities whatever, and remained in hospital for entirely social reasons. Furthermore, of the large group requiring only limited hospital facilities, 86% were fully ambulant, and 49% needed no nursing supervision in hospital. These patients would have been better off in hostel accommodation with a lower ratio of bed-space and more amenities for normal activity. As Garratt *et al.* pointed out, however, patients in this category are not necessarily well enough to live alone; on the contrary, many need to belong to an organized community which can offer them assistance with training and employment. Among patients no longer needing hospital care two main types were distinguished—those suitable for hostel accommodation and those well enough for boarding out.

The above investigations were carried out on typical mental-hospital populations, and at the time were probably quite representative. It is possible that the pattern has changed appreciably during the past three or four years. More active discharge policies, the development of special "rehabilitation units" within some hospitals, the systematic use of tranquillizing drugs, and the increase of day-hospital facilities and out-patient treatment clinics may have played some part in breaking up the chronic population of the mental hospitals. After an initial increase in the discharge rate, it is probable that advances in physical treatment have served to increase the proportion of patients with only mild symptoms, so that the proportion of patients retained for purely social reasons may have increased. This is suggested by our figures. The discharge rate for those in hospital over one year was static from 1952 to 1954, appreciably increased in 1955 on the introduction of promazine therapy, and fell to "pre-chlorpromazine level" in 1957. In 1958 the introduction of industrial therapy coincided with the highest-ever discharge rate, and this returned to "chlorpromazine level" in 1959, but went to its highest level yet in 1960 (Table I).

TABLE I.—*Yearly Discharge Rate of Those in Hospital More than One Year*

Year ..	1952	1953	1954	1955	1956	1957	1958	1959	1960
No. ..	28	29	27	40	39	31	59	39	77

Present Investigation

To test these hypotheses, and to provide an estimate of the need for mental aftercare accommodation in Bristol, it was decided to carry out a survey of the current population of Glenside Hospital (formerly the Bristol Mental Hospital), which holds the bulk of chronic psychiatric patients in the city. The Royal Commission Report (1957) proposed that in future patients suitable for mental aftercare should be the responsibility of local authorities. This view has been widely accepted in principle, but in most areas suitable accommodation does not yet exist. It will be necessary for each local authority, when planning such accommodation, to have a reliable estimate of the size and complexity of the problem.

There is one aspect, however, in which the current situation at Glenside Hospital may be of particular interest. The most significant change in this hospital in recent years has been the development of industrial work. Since a small experimental unit was established at Banstead (Carstairs *et al.*, 1956) industrial therapy has spread rapidly in mental hospitals, and there are now a large number of hospital workshops in production. Most of them, however, are still on a small scale, and the unit at Glenside is probably the largest and most productive in the country. If this form of occupation becomes generally accepted as an important factor in the rehabilitation of mental patients, as the Piercy Committee and Standing Mental Health Advisory Committee (Ministry of Health, 1958) have recommended, the growth of industrial work at Glenside, and its effect on the hospital milieu, may be an interesting augury for other hospitals.

The development of the industrial unit in this hospital, and the subsequent formation of a company—Industrial Therapy Organization (Bristol) Ltd.—has been described in a previous paper (Early, 1960). It is too soon to evaluate the effect of these projects on the pattern of patient-discharges. There can be no doubt, however, of the improvement in morale of both patients and staff, following directly on the establishment of the industrial units. For the first time a large proportion of the hospital population are fully and usefully occupied, and, perhaps more important, patients have been given the prospect of earning their living in the outside world. Not only are those patients formerly regarded as potentially capable of work now actually becoming self-

TABLE II.—*Increase in Patients' Earnings Since the Introduction of Industrial Work*

	1957	1958	1959	1960
No. of patients	1,200	1,172	1,169	1,147
Hospital workers and basic allowances	£6,820	£5,980	£6,194	£7,082
Industrial earnings :				
In hospital ..	—	£3,731	£8,706	£10,043
I.T.O. (10 months) ..	—	—	—	£7,943
Open employment ..	—	—	—	£3,750*
Total ..	£6,820	£9,711	£14,900	£28,818

* This is a rough figure calculated on the average of nine patients earning £8 a week for a full year.

supporting, but many others, once thought hopelessly deteriorated and unemployable, are now proving that they can make a useful contribution. Over the past three years patients' earnings have increased rapidly and continuously (Table II), and if the present trend continues the hospital population will soon contain a sizable proportion of wage-earners who will need only suitable accommodation to become independent and self-supporting.

Survey

The patient-survey was carried out, therefore, with particular reference to the need for accommodation and outside employment. A form was designed, covering 34 items with a possible bearing on patients' social needs. A copy was then completed for each patient who had been in hospital for at least three months continuously. (Patients under care for less than this time were excluded: short-stay patients were unlikely to present the same kind of aftercare problems.) The schedules were completed by two members of the medical staff working in close collaboration and with frequent discussion to ensure uniformity of method. Information was obtained from individual case-notes, visiting-cards, and central hospital records; by questioning the nursing staff; and by interview with patients whenever necessary. The information obtained was then transferred to Hollerith punch-cards for analysis.

Results

Age-and-Sex Distribution.—The total number of patients included in the survey was 1,012 (453 men and 559 women). A high proportion of both sexes were in the older age-groups—particularly so among the females (Table III).

TABLE III.—*Age-and-Sex Distribution*

Age	Male	Female	Total
Under 65 years ..	354	316	670
65 and over ..	99 (21·8%)	243 (43·6%)	342 (33·8%)

Patients' Status.—Only 52 patients (5.1%) were detained, the remainder were informal admissions. This represents a marked change in the hospital pattern during the past three years, the corresponding figure for 1957 being 792 (66%).

Duration of Stay.—737 patients (72.8%) had been in hospital continuously for over five years, and 862 (85.2%) had been in continuously for over two years.

Patients' Behaviour.—615 patients were rated as showing no antisocial tendencies and a further 239 only mildly antisocial behaviour, of a kind which in itself would not warrant retention in hospital. From this point of view, therefore, 854 patients (84.4%) were not in need of custodial care. It is interesting to note that, of the whole population, only 30 male and 8 female patients had any kind of criminal record; this group accounted for a large proportion of the patients still under detention. The problem of disposal of patients with a history of assault or dangerous paranoid tendencies is a real one, though relatively minor in estimating the needs of the hospital population.

Nursing Care and Supervision.—122 patients were rated as needing no nursing care whatever, while a further 355 required only the minimal supervision which would normally be provided in a long-stay annexe or aftercare hostel. From this point of view nearly one-half of the population (477 patients, or 47.1%) were not in need of hospital facilities. Furthermore, 334 patients were judged to require absolutely no restriction of movement, and a further 287 were well enough for complete freedom within the hospital grounds; these patients were all suitable for aftercare accommodation apart from their acquired dependence on the hospital regime and, in a small minority, recurrent need for medical treatment. Of the 159 patients confined to the hospital wards, a proportion were not fully ambulant, while the remainder were almost all frail, confused, or demented senile patients.

Outside Contacts.—344 patients were never visited or taken out by relatives or friends, and in 201 of these cases it was not possible to identify any possible outside support. (Of this group of patients isolated from the outside world, 84 (56 males, 28 females) were regarded as mentally normal or suffering from only mild abnormality.)

Patients' Employment.—55 patients were employed outside hospital, and 34 of these were regarded as suitable immediately for aftercare accommodation were any available; 224 other patients were engaged in industrial work in the hospital. Thus a total of 279 patients (29.3%) were being paid by outside employers. Only 372 patients (36.7%) were totally unemployed, and this number coincided largely with the senile group, which comprised one-third of the patients under survey. With regard to the fitness of individual patients for open employment, this is an aspect of prognosis on which, like most psychiatrists, we are profoundly ignorant. 64 patients were designated as fit for immediate employment; this is really guesswork, but when it is considered that most of the patients had been in hospital for over five years continuously a low figure is to be expected. Clearly there is a great need for training schemes and the provision of sheltered employment.

Type of Accommodation Required.—Only 558 patients (51.1%) were rated as needing psychiatric hospital care (and in 25 of these cases the principal diagnosis was mental deficiency). Of the remainder, 83 needed geriatric or chronic-sick hospital care, 254 required supervised aftercare, 67 were suitable for unsupervised aftercare, while 50 required no accommodation (Table IV), and were either approaching discharge or could be discharged with some pressure on relatives (one of the practical problems here is shortage of social workers). In all but the first two categories of patient—that is, those in need of hospital care—the main criterion employed was that the patient's discharge should not cause any serious disturbance of the community or undue hardship to relatives.

TABLE IV.—*Type of Accommodation Required*

	Male	Female	Total
Psychiatric care	288	270	558
Geriatric care	21	62	83
Supervised aftercare	118	136	254
Unsupervised	17	50	67
No accommodation required ..	9	41	50
Total	453	559	1,012

Of the patients regarded as suitable for supervised aftercare, 73 were 65 years or over, while of those fit for unsupervised accommodation 32 were in this age-group. Of the "supervised aftercare" group, 20 were already working out from hospital and a further 199 were being paid by outside firms for work done in hospital. Of the "unsupervised aftercare" group, 14 were working out and 49 doing industrial work in hospital. In point of fact, of the total group of patients regarded as suitable for aftercare accommodation, virtually all except a proportion of the older age-group—mainly elderly

female patients—were already engaged in some form of industrial work and earning an average of over £1 weekly.

Discussion

These results suggest that there is an immediate need for aftercare accommodation for over 300 patients, most of whom have been in hospital continuously for several years, have only mild psychiatric symptoms, and no longer need either in-patient treatment or custodial care, but who cannot at present be discharged from hospital because they have no family support and have become dependent on institutional care. Furthermore, 83 patients (21 male, 62 female) were straightforward geriatric cases not needing the facilities of a mental hospital.

To solve the problem of overcrowding, and to make economic use of medical and nursing staff, it is essential for mental hospitals to maintain an active discharge policy. If the mental hospital is allowed to continue to fulfil the functions of a hostel, and a geriatric and chronic-sick unit, this must deprive psychiatric patients of the care which is their right, and will serve only to discourage medical and nursing staff. Thus there is every incentive to discharge chronic mental patients from hospital whenever possible. The effect, however, of discharging psychiatric patients prematurely or without adequate provision may well be serious for the patients' relatives and for the community; moreover, such patients relapse quickly in a high proportion of cases. To pursue a deliberate policy of discharging chronic patients, without regard to the facilities existing for their resettlement, is irresponsible, and likely to discredit the whole concept of "open door" psychiatry. In short, although a large proportion of mental hospital patients may be regarded as not in need of hospital care, it is highly undesirable that they should be discharged on these grounds unless suitable alternative accommodation exists.

There is no clearly defined point at which the care of a chronic mental patient should be transferred from hospital staff to local authority. We believe that in the long run only joint schemes, which have in addition the co-operation and good will of local industry as well as of the major voluntary organizations, can successfully deal with the problem. If aftercare accommodation is to be provided by the local authority, hospital psychiatrists and social workers who are already familiar with the patients should participate in their supervision; similarly, hospital nursing staff should play a part in the care of those of their former patients who go to training workshops.

The term "supervised accommodation" is usually taken to mean aftercare hostels with one or more nurses in charge. While this type of accommodation has undoubtedly a part to play in rehabilitation, and may be the best attainable at present, its disadvantages must be borne in mind. Transition from chronic ward to hostel may mean simply the exchange of one institution for another, unless it is regarded as a transitory stage on the road to normal life. The problem must be conceived in dynamic terms; it is not a question of providing permanent accommodation for a large number of disabled persons, but of offering patients every facility for resocialization. If the provision of training workshops is one aspect of this programme, a second is training for normal home life, while a third is the establishment of therapeutic social clubs and the introduction of patients to existing clubs, so that the discharged patient does not spend his leisure in isolation.

It is hoped to develop in Bristol a scheme for housing discharged patients in a group of standard council houses adjacent to the hospital; from these they will attend the training workshop and later go to normal employment, and as their social recovery progresses they will move to houses, flats, hostels, or lodgings elsewhere in the city to complete their resettlement.

Although no controlled comparison has been possible so far, our impression is that long-stay patients obtain greater benefit from industrial therapy as practised here than from attending a course at the Ministry of Labour industrial rehabilitation units (Wing, 1960). The placing of discharged long-stay patients in open industry is proving easier through I.T.O. with its local contacts than through the Ministry of Labour.

How great a change may ensue in psychiatric practice from the development of social methods is a matter for conjecture. At one extreme of opinion it is held that all such measures are of necessity only makeshifts of the kind to which resort is always made in medical practice until the appearance of a specific therapy. That such specific treatment can be found for the major psychoses is by no means certain; unless or until it is found, the prevention of complete social disability, and of loss of normal contacts so often arising from psychotic illness, must be regarded as one of the most important goals of treatment. Moreover, in a large proportion of the current mental hospital population the major problem is one of institutional dependence rather than gross mental disorder, and here social measures alone can be effective.

With the development of a realistic employment and discharge policy, especially if sheltered workshops can be provided, a large proportion of hitherto unemployable chronic psychotics can reasonably hope to hold their own in the community. This will bring the overcrowding in psychiatric hospitals to manageable proportions, and will ultimately enable the development of the comprehensive hospital (McKeown, 1958). Smith *et al.* (1960) have shown that even in a large old hospital the gradual introduction of general medical cases is possible. Along these lines, the psychiatric hospitals can be prevented from becoming depositories for the aged and the chronic, the function which the old public assistance institutes fulfilled and which nobody wishes to see re-established.

Summary

The pattern of the mental hospital is changing, and must continue to change. To obtain current information on the needs of mental patients in Bristol, and in particular on the need for aftercare facilities, a survey was made of the mental hospital population. The present situation was thought to be of particular interest in view of the development of industrial therapy and the increase in patients' earning power.

The results suggest that little more than half the population require psychiatric hospital treatment; one-third are over the age of 65; one-third are suitable for aftercare accommodation of one type or another, and of this group a high proportion are potentially self-supporting.

There is urgent need for the provision of aftercare accommodation, but this must be regarded as a step on the road to complete resettlement.

We acknowledge the advice and assistance of Mr. J. A. Everingham, punch card department, South-Western Regional Hospital Board; Mr. T. Lefroy and Mr. T. Williams, of the Finance Department, Glenside Hospital;

and Mr. L. A. Miller, senior administrative assistant, Glenside Hospital, Bristol.

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WINCHESTER ADDRESS

On May 24 the Winchester Division of the B.M.A. entertained the Minister of Health, Mr. J. ENOCH POWELL, in the New Hall of Winchester College, where he delivered this year's Winchester Address. His address dealt with the relationship between doctors and politicians, and we published it in full in our opening pages last week (May 27, p. 1479) under the title "The Elephant and the Whale." Our picture this week shows the Minister with the chairman of the Winchester Division, Mr. P. R. MITCHELL.

The meeting was attended by over 400 doctors and their guests from the Division's catchment area, which besides Winchester includes Alton, Andover, and Basingstoke.

Chairman's Welcome

In introducing the Minister, Mr. MITCHELL said that as a boy at school in Edinburgh he had been encouraged to learn something, not only of the history, but also a little about those who through the centuries had contributed most to that lovely city. Whenever a distinguished guest visited the school they had been required to nominate the individual whom they felt it was most appropriate that he should meet. Perhaps because on this occasion they were privileged to meet in Winchester College—by the kindness of the headmaster—he had recalled this rather entertaining mental exercise, and had begun to wonder which of those who, in so many different spheres, had done so much for the ancient city of Winchester their most distinguished guest would have liked to meet—politician, poet, author, scholar. Their guest had all these attainments, so that even in Winchester the field of candidates was somewhat narrow. Finally, however, he had selected one to whom this city owed a considerable debt of gratitude.

[*Hampshire Chronicle*

The individual he had in mind was in the early eighteenth century a prebendary of Winchester Cathedral. In 1736, exactly 225 years ago, he, too, had delivered a Winchester Address—which must surely have been the first of its kind. It took place in Winchester Cathedral before, as the official record stated, a gathering of persons of the most consequence and of every denomination and party. Its main object was to explain the necessity for and the establishment of the County Hospital in Winchester, of which he was the founder. He thereby had given Winchester the distinction of having the oldest of the provincial non-teaching hospitals in the country. His name was Dr. Alured Clarke, and, not content with founding the Royal Hampshire County Hospital, later, when he became Dean of Exeter, he had also founded what was now the Royal Devon and Exeter Hospital. "I think our guest might have liked to meet him."

Mr. Mitchell then invited Mr. Enoch Powell to deliver the Winchester Address, which he did. At its close Dr. A. M. SMEATON, of Basingstoke, chairman-elect of the Division, proposed the vote of thanks to the Minister.

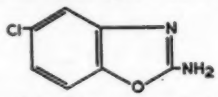
To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in common use.

Zoxazolamine

"Flexin" (McNeil Laboratories).

Chemistry. — This substance is 2-amino-5-chlorobenzoxazole and has the following structural formula:



Pharmacology.—Zoxazolamine was originally introduced as a skeletal muscle relaxant, but is now also used as a uricosuric agent in chronic gout because it inhibits tubular reabsorption of urate. In regular dosage it effectively increases the renal output of uric acid, lowering the level in the plasma, and depleting the tissues of tophaceous matter. Small doses of salicylate (1–2 g. a day) antagonize this uricosuric effect of zoxazolamine, and should not be given concurrently.

Therapy.—Administration of the drug must be continual, because plasma levels of uric acid soon rise above normal again if treatment is discontinued for even a day. Zoxazolamine is not advised for the treatment of acute gout; indeed, acute attacks may initially be precipitated by the regular use of any effective uricosuric agent. In time, however, the incidence of acute attacks diminishes in patients maintained on uricosuric therapy. The urinary output of uric acid should be kept up, and the urine should be alkalinized by concurrent administration of alkalis such as sodium bicarbonate. Acute attacks of gout may be treated by the usual agents (for example, colchicine or phenylbutazone) without discontinuing uricosuric therapy.

Weight for weight zoxazolamine appears to be some two to four times as effective as probenecid and about the same as sulfinpyrazone. It is wise to start dosage at very low levels, gradually increasing to ¼–1 tablet (125–250 mg.) 8-hourly. The tablets should always be taken with food, and plentiful fluids taken between meals. For those patients who do not respond satisfactorily another uricosuric agent may be given in addition; some patients derive more benefit from two such agents than one alone — for example, zoxazolamine + probenecid or zoxazolamine + sulfinpyrazone.

Side-effects.—These are usually mild and are relatively uncommon. Zoxazolamine may cause gastro-intestinal upsets, dizziness, drowsiness, rashes, and, very rarely, toxic hepatitis. Diminished renal function is not an absolute contraindication, but dosage in such cases should be more circumspect.

N.H.S. Basic Price.—50 tablets for 25s. 10d.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Shortage of Nurses

SIR,—Many hospitals are closing beds owing to nursing shortage, and the time therefore seems opportune to call attention to the lack of co-ordination between the authorities responsible for nurse-training and those responsible for nursing our patients.

The main interests of the General Nursing Council and the Central Midwives Board are to supervise the training and the standards of their profession. Nurses are employed to work in hospitals whilst training, and for this essential work the student nurse receives free tuition and a small salary, after deduction of a nominal amount for her upkeep. In most professions the students are supernumerary to the established staff. It follows that many of the decisions taken by the Council or Board deeply affect the working of the hospital.

It is a matter of grave concern that decisions taken by the General Nursing Council and the Central Midwives Board can be approved by the Minister without adequate previous consultation with the hospital authorities, both lay and medical. This lack of co-ordination affects particularly the non-teaching hospitals, which have the largest majority of beds in the country. Recent examples of action which have unsettling effects on the work of hospitals and possibly on recruitment are:

(1) The decision to increase the number of assistant-nurse training schools by limiting the number of hospitals, which could have a school for State-registered nurses to those which have more than 300 beds. Many hospitals will thereby be put to the trouble and expense of setting up two training schools for nurses; others will suffer from being demoted. Might it not be better to have a comprehensive training, with an ordinary and honours qualification, rather than split the nursing profession in two? Those aspiring to higher posts could, after more academic postgraduate education, be given a senior title.

(2) The practical test has been dropped from the preliminary examination, and this, together with other more stringent examination requirements, tends to exclude girls with the right personality but of borderline academic ability.

(3) The General Nursing Council and the Central Midwives Board are now pressing for an extra three months' highly theoretical training in midwifery to be inserted into the already overcrowded syllabus of lectures and demonstrations. This scheme would further deplete the general wards, would shorten the general training by giving a totally disproportionate amount of tuition in a subject which in practice would affect only a few nurses, and for which there is already a specialized diploma. It would, besides, involve a fairly large expenditure if the nurses could be found to replace those on the midwifery course. Further difficulties would accrue to many hospitals in organizing lectures and tutorials, particularly those which have the Part I Training School. Might it not be better either to have a shorter and simple programme or to extend the whole period of training by three months, possibly on a voluntary basis?

A trend towards the creation of a graduate nurse is visible. This departure from the tradition of this country is to be deprecated, both in the interests of the patient and for its financial implications. Before the hospital service is brought to a standstill by well-meaning sectional interests the Minister of Health should see that when major decisions are made affecting the nurses employed by hospitals, all those concerned are taken into consultation.—I am, etc.,

St. Helier Hospital, Carshalton, Surrey. WILLIAM N. ROGERS.

SIR,—The shortage of nurses continues to affect seriously the work and efficiency of the hospitals throughout the country. It is a shortage which shows no signs of diminishing. Much has been written and much has been said about it. Is it not now time to reconsider what must surely be a most important factor in the situation—namely, the rates of pay of those nurses in training and those who have qualified?

I suggest that action to remove this great obstacle can no longer be delayed. The poor salary which a trained nurse can command, as compared with other occupations which require a much shorter and less arduous training, must surely deter entrants to the profession.

The days are gone when nursing can be taken up as a vocation without regard to financial reward. It is right that none should be accepted for training without the right aptitude, but I do suggest that until salaries throughout the nursing profession are considerably increased the work in our hospitals will continue to be severely handicapped.—I am, etc.,

Stowmarket, Suffolk. ROGER KYNASTON.

Settlement of Compensation

SIR,—Dr. Frewen Moor (May 20, p. 1459) rightly draws attention to the lack of correspondence which has followed Dr. Henry Miller's stimulating papers on accident neurosis (April 1, p. 919, and April 8, p. 992).

The settlement of a claim for compensation should be regarded as part of the patient's rehabilitation. In the case of severe or multiple injuries some delay is essential in order that an accurate picture of the prognosis and residual disabilities may be obtained, and is, therefore, in the patient's interest. With minor injuries, particularly of the kind so ably described by Dr. Miller, prompt settlement of any claim is highly desirable, both from the angle of the patient and also of the national economy. As he points out, very few patients are actively malingering, and a delay which permits the development of a neurosis can only be harmful. To the nation, the cost cannot be calculated, but in term of money paid out in sickness benefits and National Assistance, along with the wastage of man-hours, it must be enormous.

Surely, therefore, it is urgently necessary that machinery is set up to review this problem, so that the type of claim can be sifted, and the rapid settlement of those of a trivial nature, which are unlikely to come to court, made possible. A joint commission of the legal and medical professions should be able to work out some satisfactory solution.—I am, etc.,

London W.1. J. N. ASTON.

Smart Journalism

SIR,—I refer to an article in the magazine *Queen*, dated May 10, 1961, entitled with little taste, "The Smart Gynaecologists." In an aura of crapulent nonsense the author describes the professional and social accomplishments of fourteen eminent obstetricians, including the president of the Royal College of Obstetricians and Gynaecologists, the gynaecologist to the Royal Household, and a university professor. In this article the simple (lay) reader is regaled with terms such as, "His caesarian sections are regarded as the neatest trick in the business," "She stressed he has no bedside manner," and, "He does not appear to take much post-natal interest in the babies or their mothers."

In the first place, I have not the slightest doubt that the doctors named had no knowledge of this article prior to publication, and would never lend their names to such practice, albeit elegantly performed for an elegant public. Secondly, I presume that a journal can print what it thinks fit, although this article sails perilously close to the rocky shore of libel.

But where do we go from here? If this is the dangerous precedent which I think it is, each and every provincial newspaper or periodical of the social type will proceed to feature revealing pictures of the local medical personalities, and the general practitioner will not be spared. I can see it already. "He gives the most painless injection north of London Town." "Think twice before you call him out at night." "His tonics really work!" Sir, may I make the plea that the Association make the most energetic possible representations to the Press Council, to prevent a recurrence of this revolting journalism?—I am, etc.,

Kirby Muxloe, Leicester. LOGAN MITCHELL.

Bilateral Ectopic Pregnancy

SIR,—While it is probably true that in any given general practice it is rare to see a case of a second ectopic pregnancy, it would be a pity if Dr. A. H. Bartley's letter reporting a case (April 29, p. 1252) were to lull practitioners into a false sense of security in the diagnosis of this condition. In the past year I have seen two cases of second ectopic pregnancies. One well-known textbook of gynaecology states that 5% of all ectopic pregnancies have a second ectopic pregnancy at a later date.

A case of simultaneous bilateral ectopic pregnancy would be a rarity.—I am, etc.,

Dulwich Hospital, London S.E.22. J. M. RITCHIE.

Ovarian Dermoid Presenting as Ectopic

SIR,—A Uromi-Ishan woman aged 35 was referred to me from a neighbouring hospital with a history of abdominal pain of two months' duration. The pain had failed to subside despite a period of admission and treatment in that hospital. She was a multipara-5; she had not seen her period since the onset of the pain, which was accompanied by pressure in her lower abdomen. On examination she did not look as ill as she described. The abdomen showed a firm, non-tender mass about three fingers' breadth above the pubis. There was no guarding and no rebound tenderness. There was no vaginal discharge or bleeding, and the cervix was firm. Behind the uterus, which was palpated per abdomen, was a large cystic mass. It was not tender or movable, and appeared to be attached to the uterus. The temperature was 100° F. (37.8° C.) and the pulse 120.

The period of amenorrhoea bothered me because I knew that Ishan women counted "moons." If a woman saw her period last week and a new moon appeared to-day she would tell an inquirer that she had not menstruated since last month. In short she would answer the question, "When last did you menstruate?" with "One month." So the history of two months' amenorrhoea could mean anything from a few weeks to two months. Bearing threatened abortion and ectopic gestation in mind, I admitted the patient for observation, but during the day the intensity of the pain increased and she began to vomit. The pain had become so severe by the next morning that I settled on ectopic pregnancy and decided to do a laparotomy. Under 1.5 ml. "stovaine" (amylocaine hydrochloride) the abdomen was opened to disclose a pregnant uterus (about 10 weeks) and behind it a large haemorrhagic cyst arising from the left ovary and wedged in the pouch of Douglas. There was no fluid in the peritoneal cavity. With the least of manipulation the cyst was removed and the abdomen closed. On section the mass proved to be a dermoid cyst containing a clump of hairs and recent blood clot. At one point the wall of the cyst had become so thin that a small blood-vessel had given way and from this a little blood was oozing.

On the tenth day the patient was discharged well. The pregnancy went on to term and she returned later to have a normal delivery.—I am, etc.,

Zuma Memorial Hospital, Irrua, Nigeria. XTO G. OKOJIE.

Intraperitoneal Haemorrhage from Fibroids

SIR,—The communication by Mr. Abdel Hamid Badawy (March 11, p. 717) on a rare abdominal catastrophe has a special interest for me, for I encountered a similar event some years ago.[1]

An unmarried woman aged 35 years was admitted, under my care, to the Drogheda Memorial Hospital with the following note from her doctor: "The lady, on returning from Mass, felt herself getting weak and fell on the pavement. When I saw her she looked pale, her pulse was very weak. . . . Multiple fibroids could be felt in the abdomen." When I saw her in hospital her pulse was still weak. Examination revealed generalized abdominal tenderness and rigidity. Percussion of the abdomen revealed shifting dullness. A pre-operative diagnosis was made of a ruptured follicular or luteal cyst. The peritoneal cavity was full of blood. Two large pedunculated fibroids were growing from the upper portion of the uterus. Blood was oozing from a venous plexus situated at the back and in the centre of a large interstitial myoma. The blood was temporarily controlled by the insinuation of a large pack behind the myomatous uterus. The pedunculated fibroids were rapidly amputated. The interstitial myoma was enucleated and the bleeding permanently controlled by the insertion of mattress sutures into the bed of the enucleated tumour. The patient made an uneventful recovery.—I am, etc.,

Glenageary, Co. Dublin. D. J. CANNON.

REFERENCE

[1] Cannon, D. J., *J. Irish med. Ass.*, 1953, 33, 76

Teats

SIR,—Dr. Rosemary Graham (May 20, p. 1453) is to be congratulated on drawing our attention to teats and the size of holes in them, but I was disappointed that she dismissed the vacuum problem so lightly.

Most modern infant-feeding bottles are completely closed apart from the hole in the teat. Removal of the milk by suction creates an ever-increasing negative pressure until the baby releases the teat and allows air to bubble back into the bottle. Weak, stupid, and premature babies may not learn the trick at once and exhaust themselves before doing so. This unnecessary obstacle can be avoided by using either an open-ended boat-shaped bottle or a plastic collapsible one, or best of all with an air inlet on the side of the teat. Such a teat is labelled B in Dr. Graham's photograph. I have found it most helpful in sick and weak babies, but unfortunately it is too large for use in prematures. Consequently the latter still have to struggle to extract milk from a pipette closed by a rubber bulb at the opposite end to the teat. Can anyone suggest how to let the air in during sucking without letting the milk escape when the pipette is put down to "wind" the baby?—I am, etc.,

Stock, Essex. IAN G. WICKES.

Neonatal Resuscitation

SIR,—In connexion with your leading article (February 18, p. 483) and Dr. R. J. Hamer Hodges's letter (May 20, p. 1464) on this subject, I would point out that the all-important step is to get oxygenated blood to the vital centres in the brain as quickly as possible. For this purpose, the most effective method is to inject oxygenated blood into the umbilical vein. The Italians[1] have shown that this, combined with intratracheal oxygen, gives most gratifying results, although it involves brisk and practised team-work.—I am, etc.,

East Grinstead. W. C. SPACKMAN.

REFERENCE

[1]Ferraris, G., *Minerva ginec. (Torino)*, 1960, **12**, 1221.

SIR,—After much study and 25 years' experience, I would flatly deny Dr. R. J. Hamer Hodges's conclusion (May 20, p. 1464) that, "except in the most adverse circumstances incompatible with the logical effective treatment, drug-stimulation should be abandoned as a method of neonatal resuscitation."

Sir Joseph Barcroft taught, and his observation has never been disproved, that a respiratory movement was the normal response of the foetal nervous system to practically any stimulus. Even as adults we "gasp with astonishment," and with sudden pain we make a gasp before a cry. Any viable foetus which does not breathe does not do so primarily from lack of oxygen but because the brain is not responding to the stimuli it is receiving. Therefore the "logical effective treatment" is by means of drugs to raise the cerebral threshold so that it does respond to these stimuli. And if the right drug is used the response is usually immediate, complete, and permanent.

Over the past 25 years or more I have—at first quite fortuitously—used a combination of leptazol and ephedrine ("cardiazol-ephedrine") by intramuscular, and in severe cases by intraventricular, injection with the most dramatic and successful results. It is quite the most dramatic thing to be seen in therapeutics, as full respiration is usually established in ten seconds or less. My first intracardiac case—given because intramuscular injection had produced no effect in five to ten minutes (in domiciliary emergencies one does not look at the clock)—later played centre forward for the Cheshire schools and is now a smart business man. The worst case I have had, who received 2 ml.—normally a fatal convulsive dose, though in this case it produced a relatively slow recovery, 20 minutes being required for regular respiration after fully 15 minutes' apparently lifeless flaccidity—is now a very intelligent boy at a grammar school, in spite of extensive polio paralysis when 3 years old which prevents him walking at all.

I very much doubt whether any oxygen treatment would have saved some of my cases, and the chances of mental retardment would have been much greater owing to the slower response. I have the highest regard for the work done in our research departments and hospitals, and of course I owe a lot to Sir Joseph Barcroft, but the techniques that look so wonderful on T.V. are not usually appropriate for general practice, and it is quite wrong that those who employ them should try to teach doctors and students to neglect methods that can be used anywhere and which are, in this case, more logical, more effective, and have proved over the years to carry less risk to the infant.—I am, etc.,

Winsford, Cheshire W. N. LEAK.

Plaster Collars for Unilateral Facial Pain

SIR,—Three points in Dr. A. M. G. Campbell's interesting letter on facial pain (May 13, p. 1391) should be emphasized. Firstly, this distressing pain is surprisingly common; secondly, its aetiology is obscure; thirdly, it often spreads to the neck.[1]

There is a converse point of view: while cervical splintage may relieve facial pain it may also cause it, especially in persons with predisposition. We have met patients firmly asserting that their facial pains dated from halter traction or even from wearing a cervical collar. A tearing noise may be experienced: there is a sudden stab of pain which becomes chronic.

Precautions should be taken to ensure that the mandible is safeguarded intra-orally. Edentulous persons should not be instructed to remove their dentures. If old dentures have sunk owing to ridge-resorption so that they occlude at an over-closed level, then prior to halter traction they should be built up with hard wax. Patients with natural teeth may have occlusal breakdown, or the support may be inadequate due to orthodontic anomaly: these persons also need intra-oral splintage prior to cervical extension, probably in the form of resilient plastic. Another method is to apply the traction to the maxilla, not to the mandible; an acrylic splint carries heavy wire emerging from the mouth, terminating in hooks located about the zygomatic arches; the halter is hooked on at these points.

Needless to say, cervical splintage is used in treating acroparaesthesia: in such a case it would serve no purpose, rather the reverse, if it merely resulted in pressing the mandible closer to the cranium.—I am, etc.,

Temporo-mandibular Clinic, Glasgow Dental Hospital. J. CAMPBELL.

REFERENCE

[1] Campbell, J., *Brit. dent. J.*, 1958, **105**, 393.

Headache and "Eyestrain"

SIR,—I hope that the views expressed by Mr. H. Jackson (May 6, p. 1316) may have been widely read and absorbed. Anyone who is familiar with the anatomy and physiology of seeing will agree that it is not possible to damage the eyes by using them in any circumstances however difficult.

The symptoms which arise from such use of the eyes are purely muscular in origin and the muscles concerned could not be damaged by over-use. With these facts in mind it is high time that such terms as "eyestrain," "asthenopia," etc., should be abandoned as being not only meaningless but frightening for the patient. I would suggest that the symptoms associated with the use of the eyes in difficult circumstances should be referred to as "dysopsia"—a simple word which means exactly what it says.

The public suffer from many misconceptions about the eyes. Needless fear seems to be attached to the word "astigmatism"; and if it is necessary to tell the patient that he has astigmatism, he should be told very definitely that it is not a disease but merely refers to the shape of his eye and has no other significance than the blurred vision for which it is responsible.

For many years I have taught that glasses should not be prescribed if they can be done without, and that, when they are prescribed, they should be worn as little, rather than as much, as possible. The eyes cannot come to any harm for want of glasses, and glasses are of no more significance than buses, hearing-aids, and other modern aids to living. It is sometimes said that the prescribing of weak lenses is justifiable on psychological grounds. Surely this is bad psychology. It would be much better to reassure the patient and withhold the glasses. Finally, even a squint should not be regarded as cured if spectacles have to be worn to control it, and it is surely best to correct squint by operation if glasses can then be discarded.—I am, etc.,

General Infirmary, Southport, Lancs. DAVID RANKINE.

SIR,—Sight comes, but binocular vision, like wisdom, lingers. Ophthalmology owes much to Mr. T. Keith Lyle for his work on binocular vision, and it is very pleasing when such an authority stresses the importance of a careful history (May 20, p. 1462).

To discover the common symptoms which caused my private patients, seen over a period of 30 years, to seek advice, an analysis was made of 2,000 case notes in random batches of 500 consecutive patients. The result was published in my book,[1] to which you gave such a kind review. 70% of the patients were "refraction cases"; half of those came saying, "Can't see," the other half because of various symptoms which we group together as asthenopia. Of these symptoms the commonest was headache, which they rightly or wrongly attributed to their eyes. A considerable minority were right; let Mr. Keith Lyle be assured that not all of them were wrong.

Mr. Keith Lyle wisely states that latent squint may be a cause of headaches; but we both know that marked errors of refraction, especially with some anisometropia, aggravate the heterophoria and that their correction may make full compensation possible and so relieve the headache. Mr. Keith Lyle states that in his experience the headache associated with refractive errors is due to wrong glasses. The accuracy of this statement, coming from such an authority, and published in a journal of such world-wide influence, must be challenged. When Mr. Keith Lyle has reached presbyopity (is that the word?) errors of refraction will take their place in his long list of causes of headache.—I am, etc.,

London W.1. THEODORE H. WHITTINGTON.

REFERENCE

[1] Whittington, T. H., *The Art of Clinical Refraction*, 1958, pp. 11–15. Oxford University Press, London.

Chronic Headache

SIR,—I was interested to read your leading article on chronic headache (April 1, p. 957). Many sufferers from this ailment are highly strung, hard-working individuals, who seem incapable of relaxation. They walk with a slight stoop—a legacy of poor posture while at work—and they suffer from a perpetually stiff neck.

The remedy for these cases seems to be three five-minute periods of complete relaxation a day, lying on the floor if necessary, with head supported, eyes closed, and a mind devoid of thoughts and worries. The mental relaxation produces relaxation of the spasm of the cervical muscles and consequent disappearance of headache. This relaxation is further maintained by proper posture while sitting or standing.—I am, etc.,

District Hospital, Kiambu, Kenya. N. C. ROLES.

After-effect of Desert Glare

SIR,—A great many men who were in the desert during the war complain, from time to time, of pain in the eye which they attribute to prolonged exposure to glare. I have no doubt that there is some connexion between the two, but would like to know what mechanism is involved. I know that pain of a rheumatic nature may affect the extrinsic muscles, but these would not seem to be involved. Can anyone explain?—I am, etc.,

Hitchin, Herts. G. C. PETHER.

Nitrous Oxide in Dentistry

SIR,—I would like to disagree strongly with the statement made by Dr. Gordon Wyant in these columns (May 6, p. 1321) that "the technique used by Dr. Harrison is no longer acceptable." Dr. Harrison's technique is acceptable not only to Dr. Harrison, his dental colleagues, and patients, but also to many other experienced dental anaesthetists.

I wonder whether Dr. Wyant's forthright condemnation is based upon clinical experience or theoretical considerations. All anaesthetic techniques constitute an interference with normal metabolism, and I believe that to concentrate too heavily on the possible evils of temporary oxygen restriction is to take an altogether too superficial view of the problem. Oxygen restriction is not the only cause of anoxic anoxia, and if more attention were focused on the maintenance of a completely patent airway, and less on the dials and levers, dental out-patient anaesthesia would stand only to benefit. Nor, Sir, is anoxic anoxia the only variety; the extent to which circulatory (stagnant) and histotoxic anoxia may be associated with the "many agents" in which Dr. Wyant appears to have such faith is surely worthy of some consideration.

We work so much in the physiological dark that we are forced, like it or not, to pay a great deal of attention to clinical results. I know that it is a great nuisance

to the antagonists of "gas" that the patients—in their ignorance and obstinacy—simply refuse to die or go mad. But I personally refuse to abandon either my own experience or the statistical facts for a theoretical pipe-dream. I refuse to be brain-washed into pretending to believe that temporary supervised suboxygenation is necessarily evil and dangerous, just because all the best people are taking this view—irrespective of how they are actually treating their patients. I have seen all my own children become quite markedly cyanosed when crying for their bottle, but have never let it cause me to fear for their life or reason. I have watched the very best "full oxygenation at all costs" devotees allow patients to breath-hold following intubation or extubation, without apparently becoming alarmed for their safety.

May I suggest, Sir, that if total war is to be waged against all forms of suboxygenation, it will have to be waged on a much broader front than that of dental anaesthesia? For here, at least, the suboxygenation is limited to a single or a few isolated occasions, is short-lived and expertly supervised, is not (as yet) accompanied by any postural hindrance to respiratory efficiency, and is offered to a patient who has no special need for liberal oxygenation. By way of contrast, the suboxygenation entailed in that curious practice known as "gas-air" analgesia is repetitive and unsupervised, is accompanied by considerable anatomical and postural hindrance to respiratory efficiency, is immediately followed by a long period of breath-holding and straining, so that an asphyxial element is added to the purely hypoxic one, is offered to a patient who has to cater for the special oxygen demands of a foetus whose compensatory mechanisms are often stretched to their limit, and, what's more, it doesn't even work very well.
—I am, etc.,

Chislehurst, Kent. M. P. COPLANS.

Prevention of Dental Caries

SIR,—Dr. A. J. Dalzell-Ward's letter (May 6, p. 1321) is unconvincing. The only figures quoted in his attempt to refute my warning that the addition of a very poisonous substance such as sodium fluoride (which is much more toxic than cryolite[1]) to drinking water could possibly increase the cancer-inducing potential are those from certain U.S. cities cited by Hagan *et al.*[2] Dr. Dalzell-Ward must surely know that these and other studies have been severely criticized already. Nesin[3] wrote, "a careful examination of the details of data show they are so crude, the sampling so incomplete as to reveal the complete irrelevance of such studies." Dobbs[4] in his article on safety of fluorides in water concluded, "the main evidence upon which the assumption of safety has been established has been reviewed and found to be purely speculative." In any case the time (16 years) which has elapsed since artificial fluoridation programmes have been introduced is far too short for the determination of any effect on cancer incidence. It may take a further 20–30 years to reach a definite conclusion. We must remember that it took almost 50 years to demonstrate the carcinogenic properties of β-naphthylamine, and it is extremely unlikely that anyone can ever assess what part the widespread use of this substance has played in increasing the overall cancer incidence in man.

It will require far more elaborate statistical and epidemiological investigations to prove what effect sodium fluoride will have on the cancer-inducing potential in humans when at the same time there are roughly 1,000 other alien chemicals[5] being deliberately added to food and drink and consumed like fluorides in extremely variable quantities even in "control" and "test" cities. This is a far more difficult problem than the attempt to prove or disprove that tobacco smoking is primarily responsible for the present rise in the incidence of lung cancer. How can we expect those in industry and agriculture to listen to our pleas for the curtailment of the indiscriminate dissemination of toxic chemicals when certain members of the profession are attempting to increase the toxicity of public water although there is no adequate scientific indication for this mass medication?—I am, etc.,

Institute of Pathology, Royal Infirmary, Cardiff. R. A. HOLMAN.

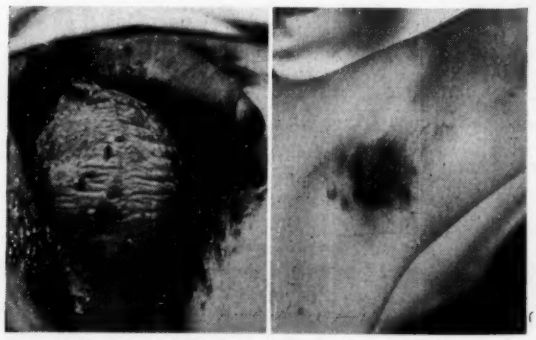
REFERENCES

1 Hein, J. W., *et al.*, *J. dent. Res.*, 1951, **30**, 466.
2 Hagan, T. L., Pasternack, M., and Scholz, G. C., *Publ. Hlth Rep. (Wash.)*, 1954, **69**, 450.
3 Nesin, B. C., *J. Maine Water Utilities Assoc.*, 1956, March 10.
4 Dobbs, C. G., *Brit. dent. J.*, 1957, **103**, 267.
5 Bicknell, F., *Chemicals in Food and in Farm Produce: Their Harmful Effects*, 1960, p. 49. Faber & Faber, London.

Autogenous Vaccinia

SIR,—Autogenous vaccinia of the male genitalia and axillae is unusual. The following short account of a case may therefore be of interest, the more so since it was accompanied by a coincidental right-sided pneumonia.

On September 22, 1960, I revaccinated a male crew member, aged 18 years, against smallpox. On September 26, clinical examination revealed right-sided basal pneumonia, which responded to antibiotic therapy and general nursing measures. By September 29 a marked



vesicular eruption was noted in both axillae, on the scrotum—extending 1½ in. (3.8 cm.) on either side, on the shaft of the penis, and on the suprapubic region; this condition extended to the gluteal folds. It is considered that the infection was carried by the patient's hands to those sites.

After some days sloughing of the skin in these regions and later erythema of the underlying tissue were noted clinically. The accompanying photographs illustrate these details. The patient was treated conservatively, and recovered uneventfully.

I am indebted to Dr. C. M. Morton, medical superintendent, Canadian Pacific S.S., Ltd., for granting permission to publish this case, and to the hospital staff, R.M.S. *Empress of France*, who so ably nursed the patient.

—I am, etc.,

Liverpool 3. P. WALSHE, Ship Surgeon.

Earl of Arran's Blood Alcohol

SIR,—On April 27, in the House of Lords, the Road Traffic Bill was being debated. The question of tests for intoxication by alcohol was under discussion. In his speech the Earl of Arran quoted certain figures for blood alcohol levels, the results of analyses which I had performed on his blood before and after he had drunk some whisky. Unfortunately, he did not make it clear that I had instructed him that these figures were to be interpreted as alcohol only after allowance had been made for blank corrections which I knew to be necessary. Overlooking this important fact, he stated that I had found 55 mg. *alcohol* in his blood although he had had no alcoholic drink for ten hours; moreover, he claimed that "no account is taken (of this) in assessing whether or not a man should be charged." This is not correct. I thought I had made it clear to him that this would be taken into account in interpreting the results. These statements naturally evoked considerable criticism from other Members of the House. Lord Taylor was particularly harsh in his condemnation of my capabilities as an analyst. His remarks are a serious defamation of my reputation, not justified by the facts, and in view of the publicity which this matter received I feel that it is important that I should have the chance to reply.

In all chemical analyses it is necessary to perform blank tests on the apparatus, reagents, etc., and apply any necessary correction to the analytical results. There are two ways of applying such a correction—either you deduct the blank reading from the test reading and calculate the balance as result; or you may calculate the total reading as result and make allowance for the blank which you know by experience to be necessary. It is perhaps unfortunate that I have chosen the latter method and misinterpretation has resulted.

I assure you that my method, when properly interpreted, is capable of quite accurate and reliable results. To prove my competence to analyse blood for alcohol content by this method, I would welcome the chance to do analyses in parallel with any forensic laboratory that my critics care to name.—I am, etc.,

Peace Memorial Hospital, Watford, Herts. R. G. BOWLER.

Safety Belts in Cars

SIR,—Dr. D. W. Hall (May 20, p. 1463) says that he owes his life to the fact that he jumped out of a car that had begun to roll down a steep embankment, and he wonders whether safety belts might cause loss of life by trapping the driver inside his vehicle under such circumstances. I am not certain that the conclusion Dr. Hall draws from his own experience is correct. Some years ago a fully loaded single-decker bus rolled down a steep embankment near Bridgend. One man succeeded in jumping out and was crushed to death by the bus, which rolled on top of him. All the other passengers survived.

I recall two other instances where vehicles have rolled down very steep hillsides and the passengers have had amazing escapes. I believe that, apart from crushing injury, death in road accidents is mainly determined by the rapidity of deceleration, and that where a vehicle rolls down a bank deceleration may be relatively slow compared with collisions. It would seem, therefore, that a safety belt would be a distinct advantage to the occupant of a vehicle that rolls down an embankment by preventing him from being ejected from the vehicle and by saving him from being flung around inside the vehicle.

This raises the more general problem of what to do when faced with imminent disaster on the road. Since it is impracticable for all passengers in vehicles to have safety belts, what advice should be given for use in emergencies such as an uncontrollable skid or imminent collision? If there is room passengers can throw themselves on the floor of the vehicle; alternatively they can draw the knees up to the chin. Have any of your readers experience of the effectiveness of either of these measures?—I am, etc.,

Bridgend General Hospital, Glamorgan. A. W. FOWLER.

Cardiac Arrest in the Consulting-room

SIR,—I was interested in Dr. Neville A. Silverston's article on cardiac arrest in the consulting-room (May 20, p. 1439), as I had a similar experience. In my consulting-room on March 3, 1961, while I was taking the blood-pressure of an Army officer, aged 45, who had been complaining of increasingly severe angina pectoris, his heart stopped. I called to a nurse in a neighbouring room to fetch a scalpel, and one and a half minutes after cardiac arrest I was performing cardiac massage through a left intercostal incision and the nurse was applying mouth-to-mouth artificial respiration. Unhappily this attempt failed to restore the heart (necropsy showed extensive myocardial infarction), but the case emphasizes the importance of all doctors being ready for this emergency, and in spite of recent suggestions of the value of "closed chest" cardiac massage—for example, in your recent annotation (November 26, 1960, p. 1582)—a sterile scalpel should be kept in readiness wherever a doctor may be working.—I am, etc.,

28 Field Ambulance, B.A.O.R. ANDREW C. SMITH.

Yoga and the Heart

SIR,—Your annotation "Yoga and the Heart" (April 29, p. 1226) prompts me to call to your attention a report[1] which describes a patient "who is able to produce cessation of the heart beat, apparently by volition alone," through complete mental and physical relaxation without any breath-holding or Valsalva manœuvre. It may be of additional interest to note that there are on record instances of voluntary acceleration of the heart,[2] and an instance of a patient with a phaeochromocytoma who was able to elevate his blood pressure by lateral trunk flexion.[3]—I am, etc.,

Memorial Hospital of Long Beach, California, U.S.A. GEORGE X. TRIMBLE.

REFERENCES

[1] McClure, C. M., *Calif. Med.*, 1959, **90**, 440.
[2] Editorial, *J. Amer. med. Ass.*, 1948, **136**, 42
[3] Ransom, C. L., Landes, R. R., and Gaddy, C. G., *J. Urol. (Baltimore)*, 1958, **79**, 368.

Leg Ulcers

SIR,—Amongst the multitude of drug advertisements that reached the general practitioners in the last week or two I found at least six local applications for use in the treatment of varicose ulcers. They included a variety of combinations of expensive antibiotics, cortisone derivatives, amino-acids, enzymes, disinfectants, and other healing charms.

In view of this high-pressure salesmanship it may be worth pointing out that the great majority of varicose

ulcers seen in general practice will heal perfectly well using a plain pressure-bandage such as "viscopaste," covered by "elastoplast," applied from toes to knee in an ambulant patient. Thus I have had in the course of the last year nine patients with varicose ulcers varying in size from 4 to 80 sq. cm. and in duration from two to 20 years. Firm bandaging applied at fortnightly intervals healed all the ulcers but one in two to four months. The exception was in a man whose ulcer had previously been grafted and had broken down again. The only important proviso is not to delegate the bandaging to nurse or patient unless these have been taught the method clearly.

There are, of course, hard-core cases that will not heal on this treatment. McAusland[1] has recently described how an antibiotic-hydrocortisone aerosol may help in these instances. However, the claim made by some firms that topical medicaments promote healing in an uncomplicated varicose ulcer seems contrary to practical experience and hard to sustain on theoretical grounds. Do surface applications of, say, amino-acids really influence the rate of granulation-tissue formation and epithelization? Or is one to give the same credulity to these suggestions as to the existence of "tonics" for hair growth?—I am, etc.,

London E.17. JOSEPH JACOBS.

REFERENCE

[1] McAusland, S., *Practitioner*, 1961, **186**, 227.

SIR,—We were heartened by the general approval of our article on leg ulcers (March 25, p. 871) expressed by Dr. A. Aitken Ross and Dr. Bernard Peck (April 22, p. 1171 and p. 1173). We enjoyed their humour and were not abashed by their criticism. We are, indeed, indebted to Dr. Peck for pointing out an inaccuracy in copying from "Martindale" (1958) the formula for eusol which we are accustomed to designate by name only, the corrected version being "a solution of 1.25 g. of boric acid and 1.25 g. of chlorinated lime in water to 100 ml." (not "to 100%" as we inadvertently recorded), and we regret the error. Regarding the formula for ichthyol calamine liniment, percentages of the active ingredient in a prescription are still popular among dermatologists here because, by their use, quantities can be recognized at a glance and easily altered to suit the stage of treatment reached. This is a facility which would be lost with more accurate and standardized prescribing.

With reference to Dr. Aitken Ross's "outmoded" drugs and methods of treatment, we can only record our experience that from time to time we have found the judicious use of copper sulphate crystals indispensable in dealing with exuberant granulations which threatened to delay healing and produce an eventual painful and hypertrophic scar. Dr. Ross will note that we purposely avoided the word "accelerates" in reference to the healing of leg ulcers, and we stressed (p. 871) that "most ulcers not grossly infected will heal eventually on any non-irritant application provided the patient is recumbent." Our conclusion was that eusol produced the fastest regression rate—that is, it allowed healing to take place under the conditions of the trial at the optimum pace. We fully recognize the dangers of too long and too strict bed-rest, but we maintain that, with proper supervision, these can be minimized, and, when healing takes place at a reasonable rate as with the majority of our cases on eusol, they are negligible. Our experience with four ulcers treated by dressings of "viacutin" (designated an antiseptic by the makers) may have been unfortunate, but, as pointed out in our first sentence under "Discussion," our method is not a reliable guide to the complete value as a healing agent of each product investigated.

Finally, we would invite Dr. Ross to inspect our wards at Stobhill General Hospital, where we have little doubt he will find that his fears regarding the complications of the recumbent posture reasonably applied are completely unjustified, and, furthermore, he may even meet some of the refugees from "special out-patient departments," their legs abraded from too heavy elastic compression or putrefying from being covered by occlusive dressings over varying periods of time, during which they have been left to "stew in their own juice."—We are, etc.,

A. GIRDWOOD FERGUSSON.
JAMES C. P. LOGAN.

Department of Dermatology,
Stobhill General Hospital,
Glasgow N.1.

REFERENCE

[1] Martindale, *The Extra Pharmacopoeia*, 1958, 24th edition, Vol. I, p. 382. The Pharmaceutical Press, London.

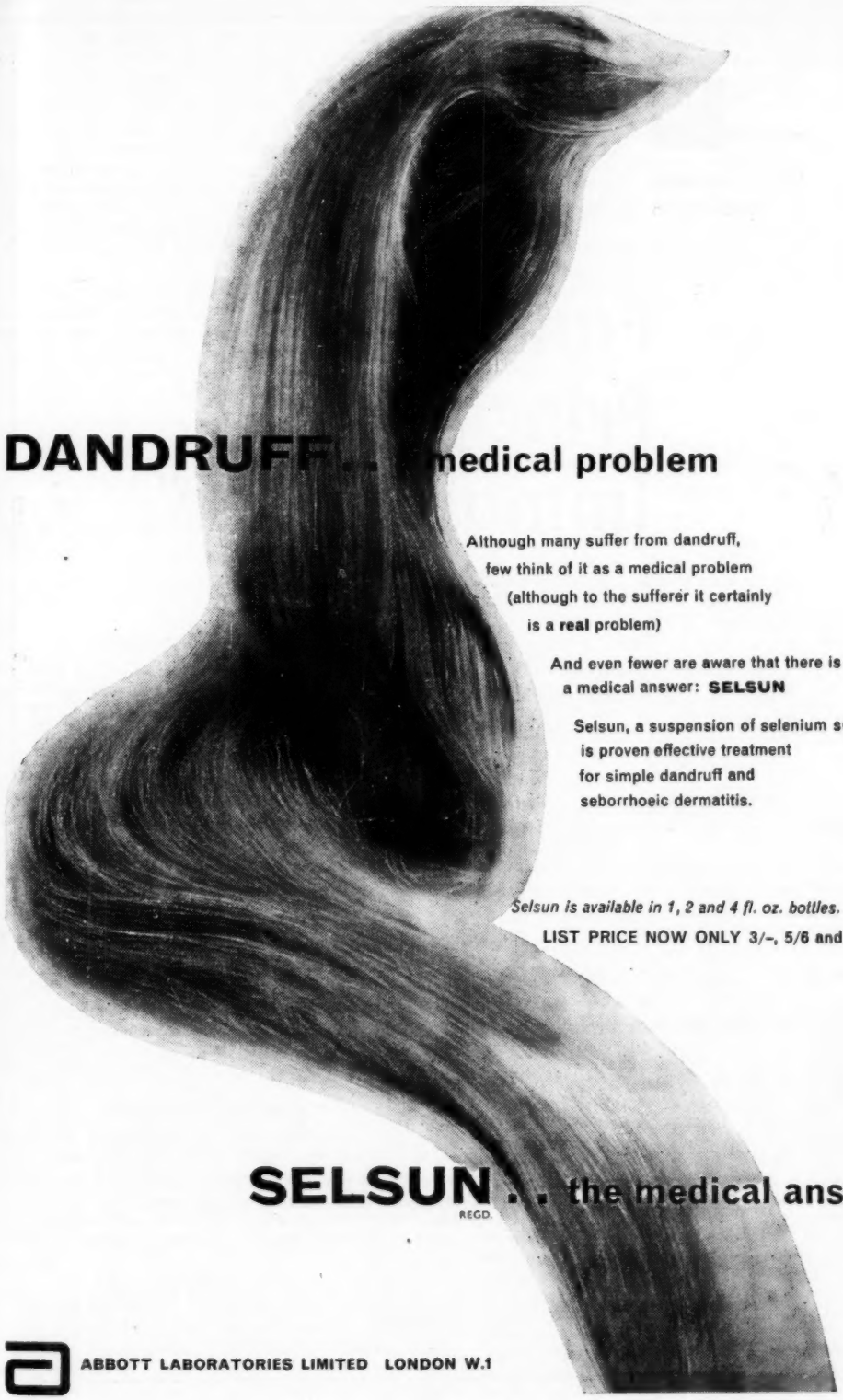
Gangrene of the Tongue

SIR,—The case of massive gangrene of the tongue caused by temporal arteritis and ably described by Drs. B. F. Brearley and J. G. MacDonald (April 22, p. 1151) is very similar to the following case who was admitted under my care in the Royal South Hants Hospital, Southampton, on May 24, 1960:

The patient was a housewife, aet. 77. The history was difficult to obtain. She had been vaguely ill since March. Ten days previously generalized headache developed with pain over the right face, accompanied by ptosis of the right upper eyelid. At about the same time the tongue became extremely heavily coated and stiff, so much so that speech was increasingly difficult. Projectile vomiting had occurred once at the onset, 10 days previously. There was no limb paresis, and further history was unobtainable.

On examination: temperature, 101.4° F. (38.55° C.); pulse, 78; respiration, 24; B.P., 136/70. Obviously in considerable pain; no drowsiness or photophobia; the tongue was swollen, very heavily coated, and black in places, and the sub-mental area was tender (there were no associated enlarged cervical glands, however). No fetor oris. Partial right third-nerve palsy with complete ptosis and inability to adduct the eye beyond the midline; both pupils equal with normal reactions. Right Babinski response. C.S.F. normal in every respect. B.S.R. 128 mm. in one hour. Haemoglobin 69%. M.C.H.C. 30.6%. W.B.C. 11,600/c.mm. (neutrophils 82%, lymphocytes 10%, monocytes 6%, eosinophils 1%, basophils 1%).

She steadily improved until June 6, when left-sided pain and hyperalgesia developed on the dorsum of the neck and the occiput. The left posterior auricular artery was by then painful, tender, and swollen. A diagnosis of temporal arteritis was made and intensive steroid therapy was initiated. By this time the right anterior half of the tongue had become completely black on both dorsal and ventral surfaces; it was obviously gangrenous. Thereafter, the pain and hyper-



DANDRUFF . . . medical problem

Although many suffer from dandruff,
few think of it as a medical problem
(although to the sufferer it certainly
is a **real** problem)

And even fewer are aware that there is
a medical answer: **SELSUN**

Selsun, a suspension of selenium sulphide,
is proven effective treatment
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seborrhoeic dermatitis.

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algesia in the neck and occiput gradually subsided, and the tongue, with the exception of the gangrenous area, gradually recovered. The gangrenous area separated completely on June 16. There was continued improvement in the tongue, and eventually it healed completely (see photograph).

Now, one year later, she is quite well with no symptoms other than some slight dysarthria. The left posterior auricular artery is not palpable, and the plantar response on the right is indeterminate. The right third-nerve palsy has recovered completely. Biopsy of the healed edge of the tongue on August 12, 1960 (Dr. R. A. Goodbody), showed fibrosis with patchy chronic inflammatory tissue consistent with damage to the blood supply, although no actual proof of this was seen in the small piece of tissue submitted to biopsy.

This case emphasizes the widespread distribution of lesions in temporal arteritis. A superficial scalp artery, a lingual artery, and one of the penetrating branches of a posterior cerebral artery were involved. I agree with Wise[1] that the case of Howard and Cremin[2] was probably also due to temporal arteritis.

I am indebted to Mr. N. A. White, clinical photographer to the Southampton Group of Hospitals, for the photograph; Dr. G. S. Graveson for his help; and Dr. Mary Edwards for referring the patient to me.

—I am, etc.,

Royal South Hants Hospital, Southampton. R. J. McGILL.

REFERENCES

1 Wise, D., *Lancet*, 1959, **2**, 674.
2 Howard, S., and Cremin, M. D., ibid., 1959, **2**, 410.

Prognosis in Schizophrenia

SIR,—As far as I am concerned Dr. Stephen Krauss's recent communication (May 13, p. 1392) is in some respects a sermon to the converted. If I have interpreted him correctly, Dr. Krauss is anxious to make the point (often made before) that the term "schizophrenia" has its generic implications, and that these should be borne in mind whenever the prognosis of schizophrenia is under consideration. This accords with my own view. In addition, he argues that many sufferers from schizophrenia need a kind of half-way house betwixt hospital and home. Here again I agree with him. Unhappily, there is a regrettable dearth of these half-way houses, and therefore the choice lies in practice between hospital and home—and will doubtless continue to do so for a long time to come. The action of phenothiazine drugs in controlling and suppressing schizophrenic symptoms may not be conducive to "good psychopathology," but it is of inestimable value none the less.—I am, etc.,

Ilkley, Yorks. J. TODD.

Distasteful Advertising

SIR,—All doctors surely must agree with Dr. W. Gover's criticisms (May 20, p. 1466). For the individual doctor there is a much simpler way of avoiding the verbal sewage than discussion with the drug firms about its purification; the firms concerned would not be eager to admit to being disgusting, wasteful, childish, or even indiscreet.

It is quite a long time since the nauseating flow was diverted past my door. To all the drug firms involved I wrote a short letter pointing out that as I was kept up to date by the visits of their representatives (I try always to give them an interview) I have no need of any advertising media by post, consequently would they please remove my name from their mailing list: this they did. The very frequent letter which comes from new or small firms is similarly coped with. The time and cost involved are trivial.

If all doctors did this a distasteful practice could be killed stone-cold without time-wasting discussion.—I am, etc.,

Southsea. J. BIRCH.

Farmer's Lung Again

SIR,—This is just to report five further cases of "farmer's lung" (April 15, p. 1110) occurring last month here in Suffolk, in farm workers shifting mouldy corn in a silo. This dusty mould had developed from inadequate drying by warmed air of wheat combine-harvested damp late last summer and stored thus in bulk as is the increasing practice. It may be of interest that the two worst cases were the only two who had had influenza some three months previously, though serology discounted any relapse. They are being described to the Ipswich and District Medical Society next autumn.—I am, etc.,

Stowmarket, Suffolk. CHARLES A. HUTT.

E.E.G.s of Boxers

SIR,—In order to satisfy Dr. F. B. Byrom's scepticism (May 6, p. 1323) I refer him to the study on the E.E.G.s of 100 young amateur boxers by Beaussart, Niquet, Gaudier, and Guislain as presented to the Twelfth International Congress of Sport Medicine in Moscow, May to June, 1958.[1,2] Dr. Edwin Clarke and I have also published our E.E.G. results.[3,4]—I am, etc.,

London W.1. J. L. BLONSTEIN.

REFERENCES

1 Beaussart, M., *Rev. Neurol. (Paris)*, 1959, **101**, 416.
2 —— Niquet, G., Gaudier, E., and Guislain, F., ibid., 1959, **101** 422.
3 Blonstein, J. L., and Clarke, E., *Brit. med. J.*, 1954, **2**, 1523.
4 —— —— ibid., 1957, **1**, 362.

Bad English

SIR,—"This unit will commence to function in respect to male patients on . . ." So begins a circular letter announcing a new treatment unit in a South of England hospital. With shame one reads beneath the signature of a doctor. How, Sir, in all sadness, can we hope for good English from the bureaucrats when we are ourselves guilty of this sort of thing?—I am, etc.,

Sherborne, Dorset. ALAN EDELSTEN.

POINTS FROM LETTERS

Oral Treatment of Diabetes

Dr. E. F. B. CADMAN (Southport General Infirmary, Southport) writes: I was interested to read the comments of Dr. S. H. F. Howard (April 1, p. 970) on my earlier letter (March 4, p. 672). I agree with his second paragraph in which he states that some glycosuria has to be tolerated more often than not in cases treated with insulin. He goes on to say, however, that the criterion of a satisfactory response to the sulphonylureas is the absence of significant glycosuria throughout the 24 hours. This may be true, but the average doctor or patient is unable to say what level represents a significant glycosuria. . . . The only "significant glycosuria" as estimated in clinical practice is that found in the fasting state, provided the bladder has been recently emptied. Hence my advocacy of the second pre-breakfast specimen, which for adequate control must be glucose-free. In most cases the "tes-tape" will do this perfectly adequately. In these circumstances, provided the patient is not having hypoglycaemic attacks, the dose of sulphonylureas is probably correct.

Obituary

Sir ALEXANDER ANDERSON, K.C.V.O., M.D. LL.D., F.R.C.P.

By the death on May 21 of Sir Alexander Anderson at the age of 76, the medical profession in Scotland, and in Aberdeen in particular, has suffered a severe loss, for he had been recognized as a leader in medical thought, a guide in the development of professional affairs, and the doyen in all matters affecting the conduct of professional life in the city. His influence in these respects had steadily increased from his return to Aberdeen after service in the first world war by his association with teaching in the University, clinical work in the hospitals, consulting practice, and social service.

Alexander Greig Anderson was born on March 31, 1885, the son of James Anderson, Mains of Annochie, Auchnagatt, Aberdeenshire. Like Sir Arthur Keith, Professor Alexander Low, and Sir David Ferrier, he came of farming stock. Educated at Robert Gordon's College and at the Universities of Aberdeen, Dublin, and Berlin, he graduated M.A. in 1905, M.B., Ch.B. in 1909, and proceeded M.D. with highest honours in 1914. Two years spent in laboratory work in pathology as MacRobert cancer research fellow formed a sure basis for his later career. He joined the R.A.M.C. in 1915, served at the Cambridge Hospital, Aldershot, and went overseas with the 43rd and 52nd General Hospitals to Salonika. He was mentioned in dispatches for his work as officer in charge of medical divisions of these hospitals. Service in Salonika formed a lifelong link with the survivors of this campaign, and Sir Alexander was a happy member of their annual reunions.

At the end of the war he was appointed assistant physician at the Aberdeen Royal Infirmary, with a close departmental association with Sir Ashley Mackintosh. He continued the neurological specialty which had characterized the Aberdeen school in continuity with Sir David Ferrier and Sir Ashley Mackintosh. "A.G.," as he then became known, threw himself into the teaching of the large number of medical students then attending the hospital, most of whom had returned from overseas service in H.M. Forces. This work he particularly enjoyed, and he looked back to those days as among the most rewarding of his life. Many of his old students and residents recollect with pleasure his Sunday evening at-homes when discussion ranged freely over many things.

Anderson had become a Member of the Royal College of Physicians of London in 1916 and was elected Fellow in 1930. Thereafter, in 1932, he became full physician to the Aberdeen Royal Infirmary with charge of wards in the old hospital. Planning was then in progress for the new hospital at Foresterhill, and he took a heavy share in the work entailed and moved up to wards on the new site in 1936, when the buildings were opened by the late King George VI, then Duke of York, and the Duchess of York. Sir Alexander became honorary physician to H.M.'s medical household in Scotland the same year and held this office until his retirement in 1955. The Queen Mother continued to be interested in his welfare in his later years.

Many duties and offices fell to Sir Alexander. He was physician to Morningfield Hospital, honorary consulting physician to the Scottish Command during the second world war, a member of the Business Committee of the General Court of the University, a Commissioner for the University of St. Andrews, a member of the Court of the University of Aberdeen, and chairman of the Old People's Welfare Council. On the University Court he did much valuable work, and a tribute was paid to him by the convener on his retirement in 1960, when he said that Sir Alexander had been an assessor for 20 years and that he had so responded to all calls upon him "as to merit his place in the distinguished roll of alumni who had dedicated their talents to the welfare of their Alma Mater."

His great interest in later years was the provision of houses and homes for old people. In this work he was associated on a national basis with the late Sir Ernest Rock Carling. In the local sphere he succeeded in collecting ample funds to establish five well-run homes for the aged, and he was closely interested in the detailed plans of an addition for which he had been largely instrumental in the collection of some £50,000. He was a member of the B.M.A.'s Committee on the Elderly and Infirm, and he held office at two Annual Meetings of the Association, as vice-president of the Section of Neurology and Psychological Medicine at Oxford in 1936 and as president of the Section of Medicine at Aberdeen in 1939.

Honours came upon him—the LL.D. of his own university in 1949; the C.V.O. in 1951; Deputy Lieutenant of the City of Aberdeen in 1952; and the K.C.V.O. in 1956. His portrait in etching by Malcolm Osborne was presented by subscription from his old students and colleagues at a public ceremony in the Art Gallery in 1950. On this occasion he said in reply that the work for the Old People's Welfare Council had been very near his heart, and he was thankful for the great support given to his efforts by the generosity of citizens and the work of members of committees.

Sir Alexander was a good churchman, was widely read, and enjoyed conversation, travel, and company. He never married, and is survived by a nephew and his two nieces, who lived with him. In his generation he was the most widely known of his professional brethren, and none sought his help in vain.—A. L.

Dr. R. L. RICHARDS writes: The sad news of the death of Sir Alexander Greig Anderson will recall many vivid memories to those who were undergraduates at Aberdeen University in the 'thirties. By all he will be remembered not as Sir Alexander but as "A.G.," for thus he was known to friends, colleagues, students, and even patients. Others will write of his academic brilliance as a young man, of his great reputation as a consultant physician, of his service to the Royal Infirmary and University of Aberdeen, and of his work for old people. To those of us who were fortunate to be medical students in that decade when he was at the height of his powers "A.G." was first and foremost a great teacher and a friend and champion of the students.

He was a man of commanding, sometimes even forbidding, presence both physically and mentally, and students looked on him with that mixture of awe and affection which they reserve for the truly great. He was a brilliant clinician of the old school and had a wide knowledge of all branches of clinical medicine. As he himself often said, he was one of the last of the general physicians in Aberdeen. Yet he was far from old-fashioned in his outlook; no one in the hospital made more or better use of the laboratory facilities than he did, and it was largely due to his influence that the department of psychological medicine was established in the Royal Infirmary. As a teacher of clinical medicine "A.G." was magnificent, whether instructing the beginnner in the methods of clinical examination or leading a group of senior students up the steps to a diagnosis in a difficult clinical problem. He was always at his best with a small group of students who used to attend his wards on a Saturday morning, not because it was part of the curriculum, but because they enjoyed the stimulating atmosphere of a ward round with "A.G." His early training with Sir Ashley Mackintosh had made him interested and proficient in neurology, and if

there was a good neurological case in the ward it was certain to be chosen as his text for the day. The history and signs would be elicited in the ward and then the group would retire to the Chief's room, where large anatomical diagrams of the central nervous system and textbooks were consulted and discussion would be free and forthright. A rare privilege on these occasions was to be present at a consultation between "A.G." and Professor (now Sir James) Learmonth. It was clear that they enjoyed the battle of wits. Sometimes one would think of a diagnosis which the other had not considered; more often the honours were even, but it was characteristic that after the diagnostic argument the question of what was to be done for the patient was always answered and one or other would return and talk to him.

On Sunday evenings "A.G." was always at home to any of his students and the residents from the hospital, and on these occasions informal discussions on any topic of the day, domestic or international, would take place. Thus did he keep himself in touch with the activities of the young. In spite of his somewhat forbidding façade, students were quick to recognize his real qualities. Probably no member of the staff was approached more often by a student who found himself in difficulties. Perhaps the fact that "A.G." himself was a son of the north-east, from which most of the students came, had much to do with this. Help was always given and always unobtrusively; only those who knew him intimately knew how often "A.G." had helped a student over some personal problem. So, too, it was to "A.G." that the young graduates would turn for guidance about their future career. They knew that they would receive not only sound advice but also practical help in the shape of a recommendation to someone who could help them in their chosen course. Thus it was that, when two or three Aberdeen graduates were gathered together furth of the north-east and the talk would turn (as it always does) to student days, one of the first questions sure to be asked was, "How is 'A.G.'?" It saddened those of us who loved and admired him to know that his last years were clouded by illness and suffering. Now he is at rest, and if we who were his students could choose his epitaph we would echo the words that were said of another great physician and teacher, Sir William Osler, "He achieved many honours and many dignities, but the proudest of all was his unwritten title 'the Young Man's Friend.'"

C. GRAY IMRIE, M.D., D.Sc., F.R.C.P.

Dr. C. Gray Imrie, who died on May 11 after a brief illness in the hospital he served so well, was senior physician of the Sheffield Royal Hospital from 1945 to 1954, and consulting physician to the same institution until the day of his death. He was 71 years of age. As a teacher, first of all in pure physiology at the University of Sheffield and for the rest of his career in medicine both at the university and the Royal Hospital, he will long be remembered and revered by his former house-physicians, registrars, and students.

Cyril Gray Imrie was born in Canada on July 10, 1889, and was a medical graduate and gold medallist of the Western University of Ontario. He was invited to Sheffield in 1920 by the late Professor Leathes to join him in the physiology department at the university there. At this time Imrie had become interested in diabetes and was one of the pioneer workers on insulin. He had, in fact, while in Canada, taught the great Banting. From physiology he gravitated into medicine, but continued for many years to lecture in pure and applied physiology at the university. In 1928 he was appointed honorary assistant physician to the Sheffield Royal Hospital, and a little later consulting physician to the Jessop Hospital for Women. He was a general physician with a special interest in diabetes and metabolic and endocrine disorders. In 1954 he retired from the active staff of the Royal Hospital, but remained interested in its affairs and in general medicine to the very end. His latter days were clouded by ever-advancing rheumatoid arthritis, but he never complained and kept going until his final illness.

He served with the Canadian Army Medical Corps throughout the first world war and was with the 4th Canadian General Hospital in Salonika from 1915 to 1917. Returning after further military service in this country to Canada in 1919, where he was appointed lecturer in pathological chemistry at the University of Toronto, it seemed likely that he would devote the rest of his life to physiology. But this was not to be. He met Professor Leathes and worked with him. Soon afterwards he was invited by him to join the staff of the physiology department of Sheffield, where Leathes occupied the chair, and from 1922 to 1945 Imrie remained a lecturer in this department in spite of ever-increasing clinical commitments. He inaugurated physiological and biochemical laboratories at both the Royal Hospital and the Royal Infirmary, and inevitably became interested in clinical medical and surgical problems. His up-to-date and investigative knowledge of physiology and pathological chemistry fitted him to view clinical medicine in a more scientific light than was the practice in those days. And so, gradually, he became a physician with a strong physiological bent. He took the M.R.C.P. in 1924, and was elected F.R.C.P. in 1932. In 1948 his own university in Canada conferred on him the honorary degree of D.Sc.

During the second world war he helped to hold the fort of clinical medicine in Sheffield. Already a victim of rheumatoid arthritis, it was no unusual thing for him to be driven at any hour of the day or night by his wife to a distant consultation. He never spared himself, and was on duty at the Royal Hospital, cheering everybody up, on those two terrible nights in December, 1940, when it seemed that Sheffield would be razed to the ground.

Imrie was a fine physician. He had a clear and quick mind, the happiest command of the English language, and a sense of humour which delighted all who came into contact with him. Had he been ill-natured, his clever tongue would have made enemies: as it was, the twinkle in his blue eyes softened many a barb. As a teacher he was a success and at times quite inspiring. In his early days his teaching was on strict physiological lines, but later on, and especially towards the end of his career, his humanity and experience enriched his theme and one felt that this was English medicine at its best.

He had, like most successful men, a happy family life. He married Margaret Wilkinson, who, as the daughter of a distinguished otologist (the late George Wilkinson, F.R.C.S.), was cradled in medicine. She survives him, as do their two children—Dr. George Gray Imrie, who emigrated to Canada a few years ago, and Jill, who married Mr. P. A. Reid and remains in Sheffield.—T. E. G.

H. B. Y. writes: A truly "learned physician," "Cy" Imrie had a special knowledge of the aspects of medicine in which biochemical factors were so vital. He developed a huge, efficient diabetic clinic and had a wide experience in electrolyte and fluid balance and, in later years, steroid therapy. A true friend to his patients, he was a wise counsellor and tutor to all who served under him. He always gave of his skill and time unsparingly. Never was he too busy to give help when it was sought. In his final years on the consultant staff this meant more to him than it would have done to a fit and healthy physician. In overcoming the restrictions imposed upon him by rheumatoid arthritis he showed the greatest courage and stoicism which were the

admiration of his friends and professional colleagues. His fortitude had to be seen to be believed.

In spite of his busy professional life, he was an excellent and regular committee man. His opinions were invariably sound and logical and of inestimable value. After his presidency of the Medico-Chirurgical Society he had the happy thought of presenting a chain of office to be worn at society meetings by succeeding presidents. And by many unseen and intangible thoughtful acts will he be remembered by his colleagues—past and present. His loss is most grievous.

Cy Imrie was never known to say a word in anger to anyone. A true practising Christian, he bestowed kindliness and compassion on the sick and suffering. He showed us all how a great man can inspire by the way he carried his cross without complaint. As a young man he was known to all as "Beau Imrie." To the bitter end he proved himself worthy of this appellation. Our sympathy goes out to his wife, son, and daughter. Without the care and self-sacrifice that Margaret so willingly gave him, he could never have continued "in harness," notwithstanding his supreme determination. His son George left a busy practice in Canada and flew to be with his father in his final illness.

How truly can we say of Cy Imrie: "The strife is o'er, the battle done: now is the victor's triumph won."

H. D. writes: During the war years when I was associated with Dr. Gray Imrie he was almost entirely responsible for the work done in the medical wards while his colleagues were away on war service. During this time he was severely incapacitated by his arthritis, but managed to carry on a busy private practice, to attend regularly at out-patients in Sheffield and Barnsley, and in particular to supervise his diabetic patients in his clinic in the most painstaking manner. He was popular as a bedside teacher, and, although feared by the more slow-witted for his ready wit and repartee, his apt phrase and succinct comment helped many a student over the early difficulties of clinical medicine. His complete fearlessness and his attitude to his own discomfort, which at times must have been excruciating, endeared him to his staff and in fact to all who worked with him. He was an inspired teacher and a strict task-master, but also an example to his juniors, who mourn the passing of a fine doctor and a good friend.

D. P. SUTHERLAND, M.B., B.S.

Dr. D. P. Sutherland, formerly senior tuberculosis officer in Manchester, died on May 5, aged 78.

Donald Platt Sutherland was the son of a general practitioner of Ardwick in Manchester, and received his early education at the Manchester Grammar School. He then entered Owens College and graduated M.B., B.S. (London), with gold medal in medicine and pathology, in 1905. After holding junior resident appointments at the Manchester Royal Infirmary and the Townley Hospital in Bolton, he was appointed resident medical officer at the Manchester Hospital for Consumption and Diseases of the Throat and Chest, Bowden, Cheshire. In 1912 he was appointed tuberculosis officer to the City of Manchester, and held this appointment until July, 1948, when he retired. On his appointment he served for several years under the direction of the late Dr. James Niven, one of the "great old men" in the specialty. At first he worked in a small room above the then public health office, but in a short while the budding tuberculosis department was transferred to the Manchester Hospital for Consumption in Hardman Street, and an annexe was built to house the medical, health visiting, and administrative staff. Thus from the very early days he was able to achieve the integration of the diagnostic, preventive, and therapeutic services under one roof.

With the increase of work and of medical staff he was designated as senior tuberculosis officer. About this time he also became the visiting consultant physician to several sanatoria in the north-west, and was particularly interested in Barrowmore Hall, where a tuberculosis colony was in existence. Thus he became a well-known national figure in the world of tuberculosis. He was an active member and sometime chairman of the Joint Tuberculosis Council; he was a founder member and an early chairman of the North-Western Tuberculosis (now Thoracic) Society; and in 1929, when the Annual Meeting of the B.M.A. was held in Manchester, he was the president of the Tuberculosis Section. He was also lecturer in clinical tuberculosis at the University of Manchester and to the trainee health visitors at the Manchester School of Technology.

As a clinician, Sutherland belonged to the old school. A man of keen judgment and great acumen, he relied to a large extent on careful history-taking and on a scrupulous clinical examination. As an administrator he was clear-headed, cool, and firm, a strong believer in the unity of clinical and preventive measures and at times impatient of chairborn administration. He was much appreciated by the family doctors of the town, who made great use of the facilities provided, and he insisted in no uncertain fashion that they be supplied with prompt and concise reports on all patients sent or followed up at the clinic. Sutherland was also responsible for a thorough follow-up system and for helping those patients requiring financial assistance.

In the inter-war years the department developed quickly, and to Sutherland's major achievements can also be added his advice to the city council to erect a children's sanatorium in Abergele, which was completed in the late 'twenties, and the erection of a new chest clinic facing the Manchester Royal Infirmary, which was opened in 1932. Medical appointments to his staff were much sought for, and many consultant chest physicians of to-day, both at home and abroad, owe a great debt to "D. P. S." for their training and early experience.

A keen motorist, investing his early earnings in temperamental motor-cycles and cars, he was also an enthusiastic fisherman and caught many a trout in the lochs and streams of his beloved Sutherland. He had been in failing health for some years and died in Llandudno Hospital after an operation. He is survived by his widow, to whom all who knew him extend their heartfelt sympathy.

Dr. G. LISSANT COX writes: Lloyd George's Insurance Act of 1911 provided "sanatorium benefit" for insured persons and a stimulus to local authorities. Some went ahead in the diagnosis, prevention, and treatment of tuberculosis. Manchester was early in the field, as was Liverpool. Both had tuberculosis officers at work in 1912. Dr. Hawksley, of Liverpool, died young, but D. P. Sutherland played a long innings for Manchester and preventive medicine.

Clear-headed and stubborn, he put Manchester in the van. A good team was created, the clinic and hospital sides of the work more united than in most areas, and he himself had a university post. Opposite the Manchester Royal Infirmary a large central clinic was built—for long without an *x*-ray plant. This strange omission was stoutly upheld by Sutherland because an *x*-ray department existed over the road in the R.I.

Sutherland did valiant work in several fields. A good chairman of the Joint Tuberculosis Council, he was also a member of the old advisory committee on tuberculosis to the Minister of Health, and also director of the Barrowmore Settlement near Chester, the Papworth at a distance—a considerable distance—of the north-west. A strong individualist, and tough like the Sutherland granite, he served the old chest service well.

J. N. COLLINS, M.D.

Dr. J. N. Collins, honorary consulting surgeon to the Peterborough Memorial Hospital and one of the first Fellows of the British Medical Association, has died at his home in Peterborough, aged 92.

A Londoner by birth, though he never forgot his Irish origins, John Norton Collins qualified from the London Hospital in 1890 and then served as house-surgeon, house-physician, and resident accoucheur there, proceeding to the

degree of M.D. in 1893. As student and doctor he thus spanned three-quarters of a century, and to the end was fond of recounting tales of the great men of the London whom he had served as resident. After a short spell in Australia he settled in practice in Peterborough in 1898 and the next year commenced his long association with Peterborough Hospital. Elected first as honorary physician, he soon transferred to the surgical side, which was his real love, and built up a consultant practice over a wide area in addition to his general practice in the city. He was one of the first practitioners to possess an *x*-ray installation, acted for a time as medical officer of health, and, for full measure, was doing ophthalmic work up till a few years ago.

An ardent member of the B.M.A.—the issue of the *Journal* published two days before his death was found on his desk, opened and obviously read—he had been president of the Cambridge and Huntingdon Branch and chairman of the Peterborough Division. He was honorary secretary of the panel committee throughout its existence and of the local medical committee till 1958, and his membership of the insurance committee and of the executive council was likewise unbroken—surely a unique record.

A generous benefactor of the hospital, he was chairman of the medical board from 1906 to 1948, and it was mainly due to his persistent advocacy that the hospital was moved to its present site. It was only fitting, therefore, that a ward was named after him. In an *annus mirabilis* just before the close he received, in addition to the B.M.A. Fellowship, the Papal medal Pro Ecclesia et Pontifice and the Freedom of the City of Peterborough.

He was a widower for 36 years, his wife having died after only five years of marriage. There were no children and he leaves no blood relation.

W. M. writes: In his day Dr. Collins was a brilliant operator who inspired devotion from his patients despite a manner which could sometimes be blunt but concealed an innate kindliness. He was utterly devoid of self-seeking and ever ready to give help to younger colleagues all through his extraordinary career. Erect and active to the end—he journeyed to London on his own a fortnight before his death—he held a unique place in our affections. Nestor has gone. We will never see his like again.

Medical Notes in Parliament

LORDS MAKE EXTENSIVE CHANGES IN BLOOD TESTS BILL

[FROM OUR PARLIAMENTARY CORRESPONDENT]

The Affiliation Proceedings (Blood Tests) Bill which the House of Lords expects to send to the Commons soon after Parliament returns from the Whitsun break is a very different text from that which Lord AMULREE presented for second reading. It has two new clauses, and one greatly enlarged, and has lost seven of the original 11. The substantial alterations are that blood tests at the request of the mother are excluded, and that the proposed Blood Tests Board to assist the Lord Chancellor in making rules governing the tests has been dropped. These changes together mean that the Bill has virtually been rewritten, and, although it is stated that this has been done with the help and advice of the Home Office, the alterations brought some demur that they were so extensive as to constitute an abuse of procedure.

Discarded Clauses

One spell of about seven minutes during the committee stage on May 9 produced in summary form something like this:

Clause 2—deleted because the conditions in which tests must be carried out are now to be prescribed by rule. *Clause 3*—deleted because provisions relating to the admission of certificates in evidence are included in new subsections (3) and (4) of Clause 1, or are to be prescribed by rule. *Clause 4*—replaced by the provisions about costs in the amended Clause 1, or covered by general provisions in this Bill and the Magistrates' Courts Act, 1952. *Clause 5*—replaced by appeal provisions in subsection (5) of Clause 1. *Clause 6*—replaced in part by a new clause, which gives the Home Secretary power to make regulations, or covered by the existing power of the Lord Chancellor (as expanded in subsections (3) and (4) of Clause 1) to make rules governing magistrates' courts procedure. *Clause 7*—no longer necessary, because on procedural matters the Lord Chancellor already has the assistance of the Rules Committee, and on other matters the Home Secretary will take expert advice without the need for the cumbersome apparatus of a Blood Tests Board.

Advice on Regulations

One of the new clauses, intended to follow Clause 1, and entitled "Power to Prescribe Nature and Conditions of Blood Tests, etc.," was introduced to take the place of part of the original Clause 6. It was thought appropriate, Lord Amulree said, to have two separate powers to fulfil the working arrangements of the Bill, because the objects were slightly different. The Lord Chancellor's powers to prescribe procedural rules for magistrates' courts were included in the amended Clause 1. The Home Secretary's powers were to make regulations about the actual carrying out of the tests, and by subsection (2) of the new clause he was required, before making regulations, to "consult such persons or bodies of persons as appear to him to be requisite." This was agreed to.

The other new clause dealt with the enforcement of directions, and, while corresponding to the latter part of the original Clause 1, incorporated also a "conscience clause" providing that a mother should not be penalized if she had reasonable and genuine grounds for objecting to complying with a direction of the court. Although left in general terms as "without reasonable cause," Lord Amulree had no doubt that it would give a mother applying for an order full protection if there was reasonable ground.

Permissive Action

The principal change was effected by the redrafting of Clause 1. Lord Amulree proposed an amendment which would provide that a court hearing an application for an affiliation order "may, at the request of the mother . . . and shall at the request of the alleged father," give a direction for the use of blood tests. His object in so doing was to remove the phrase previously employed "by order," and thus relieve the parties from the substantial penalties which a formal order of the court would automatically attract. Earl BATHURST, Under Secretary, Home Office, added to this a further amendment to delete from Lord Amulree's draft the words "the request of the mother . . . and shall." The effect of this, he said, would be to take the mother right out of the clause, since blood tests could not help her in any way. If for any reason the court should see fit to exercise its discretion and order a test, it was left with the permissive "may" instead of the obligatory "shall." Lord AMULREE agreed that the mother should be excluded from the clause, having, as he said, always had great doubts whether it was right to keep in the mother, but accepted the removal of the obligatory "shall" only with great reluctance, because in his opinion it took away a little of the sharp edge of the Bill which might be important if there were a recalcitrant bench of magistrates. Earl Bathurst's amendment was accepted and Lord Amulree's amendment with this change agreed to.

Certificate of Results

The clause was also substantially altered by the removal of the phrase "if the mother refuses the court shall dismiss the application," for which was substituted a provision that the court "may at any time revoke such direction previously given," and the addition of five new subsections embodying provisions from the succeeding clauses as originally drafted, with some new material.

The power to revoke a direction, Lord AMULREE said, would give the court power to dispose of the direction if blood tests were not to be used. It would also be used if the mother produced a good reason for not undergoing a test. The new subsection (2) dealt with costs. Subsection (3) replaced in more generous form the original provisions of Clause 3, and simply required the court to take account of a certificate giving the results of blood tests. It provided, however, that these results should not be regarded as corroborative of the mother's evidence. This was in accordance with the expert advice he had received, as in the present state of medical knowledge tests could not show that a particular man was the father. Subsection (4) replaced another provision of Clause 3 by making provision for evidence of a blood sample to be given in the form of a certificate. Subsection (5) corresponded with the original Clause 5, except that the power of quarter sessions on appeal to duplicate blood tests already taken disappeared. Subsection (6) prevented a court from giving a second direction for a test in the same case, which would merely cause delay and expense. All these changes were accepted. The penalty clause was deleted and some consequential amendments were made in the interpretation clause.

Precedent Rejected

One alteration proposed by Lord Amulree was rejected. It was a new clause entitled "Power of Court to Require Blood Tests without Request of Party." It was a long clause, having four subsections, and some of its provisions were originally in Clause 1. Lord Amulree explained that its purpose was to enable a court to order blood tests of its own motion. If the alleged father did not ask for a test himself, the court could do so. Earl BATHURST objected to this, maintaining that a court should not have power of its own motion to order a special kind of evidence which would benefit only one of the parties, the alleged father. Lord AMULREE was not convinced that the power might not exist usefully in the background, but allowed the clause to be negatived.

Medico-Legal

SOMNAMBULISTIC HOMICIDE

[FROM OUR LEGAL CORRESPONDENT]

A recent murder trial and acquittal has revived interest in acts otherwise criminal committed while the actor is asleep. Dr. Edward Podolsky, of Brooklyn, has now written an article examining the nature of such somnambulistic acts and collecting some striking examples of somnambulistic homicide.[1]

Dr. Podolsky describes somnambulism as a state where activity is organized by a greater or smaller part of the personality dictating the general behaviour, but without any awareness, the rest of the normal personality becoming incapable of consciousness for the time being and having no influence on conduct. There is a complete dissociation of behaviour patterns from patterns of awareness. Somnambulisms are similar to fugues and other automatisms except that they appear to develop while the individual is sleeping. One of the most striking features of the examples cited by Dr. Podolsky is the ability of somnambulists to remain in a state of unawareness despite, for instance, the noise of revolver shots or the self-infliction of serious wounds.

Lack of Awareness Good Defence

Somnambulism, like automatism, must, when proved, be a good defence to a criminal charge, because the acts done take place outside the awareness and conscious will of the individual and there is thus no *mens rea*. Dr. Podolsky does not discuss the legal position of the man who knows he is a somnambulist and knows that he has a tendency to, say, somnambulistic homicide (e.g., if he has been told of a thwarted somnambulistic attack on his wife). Is not that man morally guilty if he fails to take any treatment and subsequently commits a somnambulistic homicide? Such guilt would lie, of course, in the failure to take treatment rather than in the somnambulistic act itself. In the present state of the law, such a man might be liable in civil law in negligence to pay damages to his victim or his victim's relatives, but he could not be made liable criminally.

Failure to Take Treatment

It may be that the time is ripe for the creation of criminal liability for the negligent failure to take treatment for any physical or mental ailment known by the sufferer to create in him a tendency to crime and which results in his committing a crime. A limited approach is made to this in the criminal liability of the man who is "drunk in charge," but a general provision applicable to all situations and all ailments, whether self-induced or otherwise, would be needed. Such a general provision would allow a more logical treatment of cases of "irresistible impulse." At present "irresistible impulse" is no defence in our criminal law, for obvious reasons of expediency. But, if the proposed offence of negligent failure to take treatment existed, it would be possible to allow "irresistible impulse" as an absolute defence to the positive criminal act, while imposing liability for the omission to get treatment if there could be proved to have been the feature of awareness of probable consequences. Thus, the respectable middle-aged lady who became a kleptomaniac, and was aware of her failing yet did nothing about it, would not be found guilty of stealing but could be found guilty of negligent failure to take treatment.

Indeed, the principle is capable of an even wider application. Many offenders break the law largely because they are the slaves of their antisocial psychology, and to that extent they lack moral responsibility for their crimes. Yet most of them know that the law and society generally disapprove of their behaviour, and still they wait until they are apprehended for a crime before saying, "I couldn't help it. I ought to see a psychiatrist." As we progress towards the state of treating such criminals rather than punishing them, so ought we also perhaps to progress towards the complementary Erewhonian state of punishing sick people—with this proviso, that we should punish only those who know they are sick (and know that their sickness creates in them a tendency to criminal action), who fail to take treatment, and who as a result commit an offence against our present criminal code.

Medical Implications

These views are only a starting-point. Clearly, if they were accepted, a radical reassessment of our criminal law and a rationalization of our muddled attitudes towards crime would be needed. Present penology is an attempt to impose enlightened scientific views on a system largely incapable of assimilating them: yet, before we do away with the old, much thought would have to be given to the numerous difficulties involved in the new. The views expressed above are those of one lawyer. Doctors will first of all find difficulties in accepting the thesis that the sick or unbalanced should take treatment under threat of the law. Moreover, if treatment is being taken for, say, kleptomania, would regular attendance at the psychiatrist's amount to a licence to steal? Further, is enough known about the nature of illness which causes crime? (It is not for a moment suggested that all or even most crimes are caused by illness.) While the recurrence of somnambulistic or automatist crimes may in some cases be predictable, and while the same may be said of kleptomania, how far can such prognostication be extended to other abnormal mental states? Some thinking along these lines might, however, be done with advantage.

[1] Podolsky, E., *Med. Sci. Law*, 1961, **1**, 260.

Vital Statistics

Diphtheria in Camberwell

On May 8 a child of 9 years—a pupil at a small church school in the Metropolitan Borough of Camberwell—was notified as a case of faucial diphtheria (the organism was identified as *C. diphtheriae gravis*). Since then, after the routine swabbing of the pupils at the school, 15 others have been found to be harbouring the organism, and 2 of these were clinical cases. In addition, contact cases occurred in the father (aged 46) of one child, in the sister (aged 12 and a pupil at another school) of another, and in the sister (aged 4) of a further child. In all, there have been 5 clinical cases and 14 carriers. Despite the presence in this outbreak of the *gravis* organism, all the cases are of minimum severity.

The original patient, one of a family of 8 children, in whom there is no clear record of immunization, is now believed not to have been a clinical case, but three other members of her family have been admitted to hospital. In 4 other families more than one carrier has been brought to light. Swabbing of the home and school contacts has not revealed any further carriers or cases since May 20. It has not been possible to trace the source of the infection.

In only one case is there a record of recent immunization—a child of 4 who had three injections at the age of 10 months and was subsequently recorded as Schick-negative. This child has mild nasal diphtheria.

As a result of the immunization drive after the outbreak of diphtheria in another part of the Borough of Camberwell in December, 1960, and January, 1961, it is believed that the protection rate is now very high, particularly in the school affected, and it is hoped that the present outbreak (which has no connexion with the previous one and is so far limited to pupils in one school and their family contacts) will remain circumscribed.

Infectious Diseases

Areas where the numbers of notifications were high in the latest two weeks for which figures are available.

Measles	Week Ending May 13	Week Ending May 20
Devonshire	316	**620**
Plymouth C.B.	112	**276**
Plympton St. Mary R.D.	10	**120**
Dorsetshire	156	**349**
Gloucestershire	942	**1,138**
Bristol C.B.	518	**506**
Hampshire	728	**703**
Portsmouth C.B.	279	**244**
Northumberland	656	**639**
Newcastle upon Tyne C.B.	264	**297**
Somersetshire	335	**557**
Bath C.B.	101	**202**
Staffordshire	1,384	**1,552**
Stoke-on-Trent C.B.	341	**338**
Suffolk	246	**352**
Warwickshire	891	**986**
Birmingham C.B.	532	**488**
Yorkshire West Riding	2,257	**1,810**
Leeds C.B.	285	**290**
Monmouthshire	549	**656**
Newport C.B.	299	**284**

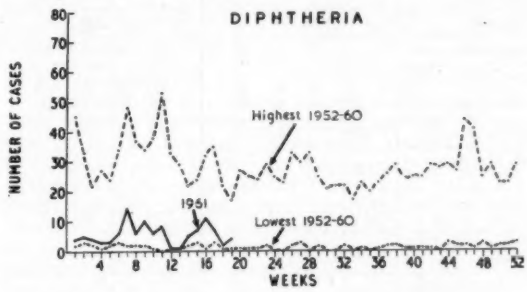
Industrial Accidents and Diseases

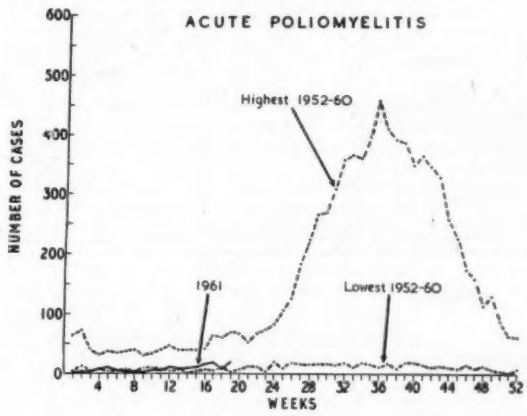
The number of workpeople (other than seamen) in the United Kingdom whose deaths from accidents in the course of their employment were reported in April was 81, compared with 104 in the previous month and 70 in April, 1960.

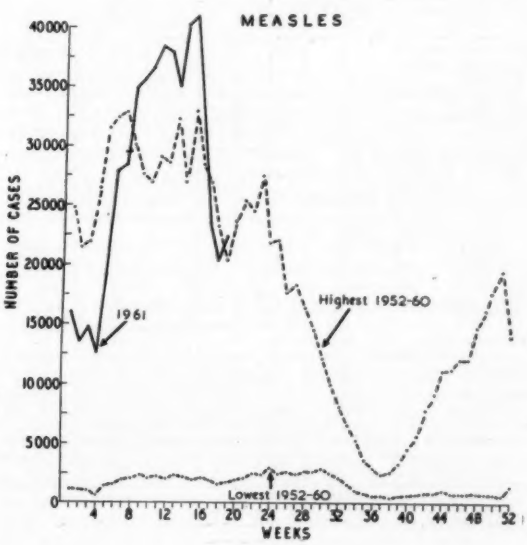
The numbers of cases of industrial diseases in the United Kingdom reported during April were as follows: lead poisoning 9, aniline poisoning 1, anthrax 1, epitheliomatous ulceration 6, chrome ulceration 23; total 40. There were no deaths.—*Ministry of Labour Gazette*, May, 1961.

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1952–60 are shown thus ------, the figures for 1961 thus ———. Except for the curves showing notifications in 1961, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.







INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **May 13** (No. 19) and corresponding week 1960.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1961					1960				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	4	1	2	0	2	1	0	1	0	
Dysentery ..	458	44	122	9	9	1,038	129	227	18	4
Encephalitis, acute	0	0		0		0	0	0	0	
Enteric fever:										
Typhoid ..	3	0	0	0		2	0	0	0	1
Paratyphoid ..	17	0	0	0		2	0	0	0	
Food-poisoning ..	615	17	7	0		156	33	15	1	
Infective enteritis or diarrhoea under 2 years				9	18				16	25
Measles*	22,434	937	425	363	192	1,749	93	42	5	12
Meningococcal infection	10	0	4	0	1	15	1	9	4	
Ophthalmia neonatorum	16	1	3	0		24	2	3	0	
Pneumonia† ..	195	14	167	2		290	9	187	6	2
Poliomyelitis, acute:										
Paralytic ..	14	0	0	0	1	1	0	1	1	4
Non-paralytic ..	5	1	2			2	0	1		
Puerperal fever§ ..	158	28	10	0		178	24	13	2	
Scarlet fever ..	445	39	24	23	6	589	30	55	16	17
Tuberculosis:										
Respiratory ..	470	58	78	15		457	43	79	17	
Non-respiratory	85	7	12	3		62	7	10	5	
Whooping-cough	680	25	70	7	32	1,362	121	266	1	39

DEATHS	1961					1960				
	Eng. & Wales	Lond	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	0	0	0	0	0	0	0	0	0	0
Dysentery ..	2	0		0		1	1	1	0	
Encephalitis, acute		0			0		0			0
Enteric fever ..	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	8	0	1	0	0	10	0	1	0	0
Influenza	6	0	0	0	1	19	1	6	0	0
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	0				0	0		
Pneumonia ..	418	36	13	11	2	601	39	18	14	10
Poliomyelitis, acute	3	0		0	0	1	0		0	0
Scarlet fever ..		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory ..	44	5	8	0	0	68	6	4	2	1
Non-respiratory		0		0	0		0	0	0	0
Whooping-cough	0	0	0	0	0	0	0	1	0	0
Deaths 0–1 year ..	297	31	19	8	6	306	28	29	7	13
Deaths (excluding stillbirths) ..	9,264	747	588	116	146	10,214	825	600	128	200
LIVE BIRTHS ..	16,077	1358	1039	300	404	16,003	1333	1048	282	459
STILLBIRTHS ..	308	30	15			308	28	30		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Chair of Obstetrics and Gynaecology, Leeds University

Mr. J. S. SCOTT, lecturer in obstetrics and gynaecology at the University of Liverpool, has been appointed to the chair of obstetrics and gynaecology at the University of Leeds from October 1. He succeeds Sir ANDREW CLAYE.

Mr. Scott was educated at Glasgow Academy and the University of Glasgow, where he obtained the degrees of M.B., Ch.B. in 1946, and M.D. in 1959. From 1947 to 1949 he served with the Royal Army Medical Corps in the United Kingdom and West Africa, and between 1949 and 1956 he gained experience in all aspects of obstetrical and gynaecological practice with teaching units in Glasgow, London, Birmingham, and Liverpool. He obtained the Diploma in Obstetrics of the Royal College of Obstetricians and Gynaecologists in 1951, and became a member of the Royal College in 1953; in 1959 he became a Fellow of the Royal College of Surgeons, Edinburgh. Since 1954 Mr. Scott has held appointments at the University of Liverpool: from 1954 to 1956 as tutor in obstetrics, when he was awarded the Ethel Boyce Research Fellowship in Gynaecology, and since 1957 as lecturer and later senior lecturer in obstetrics and gynaecology. In 1958 he was elected William Blair Bell Memorial Lecturer of the Royal College of Obstetricians and Gynaecologists, and in 1959 he was awarded the Leith Murray Prize for Research and a Wellcome Trust Research Travel Fellowship to visit and read papers at medical schools and universities in the United States. In 1960 he was awarded the Edgar-Gentilli Prize of the Royal College of Obstetricians and Gynaecologists.

Conference of Editors of Medical School Journals

A conference of editors of medical school journals was held on May 27 at the Royal Army Medical College, Millbank. The commandant, Major-General W. R. M. DREW, opened the proceedings, and he and other members of the staff of the college not only took part in the conference but acted as hosts to the student editors at lunch and tea in the R.A.M.C. Headquarters Mess. During the morning session talks were given by Sir FRANCIS WALSHE, F.R.S., Dr. A. COOKE, and Dr. W. A. R. THOMSON, and in the afternoon there was a discussion on the problems which face the editors of medical school journals. Major-General R. E. BARNSLEY, honorary curator of the museum, and Mr. DAVIES, librarian, arranged an informative and interesting exhibition in the library of the college specially for the occasion. The day ended with a dinner at the Royal Society of Medicine given by the editor and directors of the *Practitioner*.

Harveian Society of London

The Buckston Browne/Gray Hill dinner of the Harveian Society of London was held at the House of Commons on May 24, with Dr. EDWARD R. CULLINAN, the president, in the chair. The toast to the Harveian Society was most appropriately proposed by Mr. RICHARD COSTAIN, Member of Parliament for Folkestone, the town where William Harvey was born. In reply, Dr. Cullinan mentioned that the work of restoring the tower of Hempstead Church, Harvey's burial-place, was nearing completion: £7,500 had so far been subscribed to the cost of this, £3,000 coming from the United States. Later in the evening Mr. A. DICKSON WRIGHT described the progress of the work at Hempstead Church in greater detail, saying that the total cost would be £14,000. The health of the guests was proposed by Dr. C. S. TREIP, and Sir RUSSELL BRAIN replied.

International Academy of Pathology

Divisions of the International Academy of Pathology are now being formed in various countries, and the inaugural meeting of the new British Division was held at the Royal College of Surgeons in February. Professor C. V. HARRISON was elected as president, Professor N. H. ASHTON as president-elect, Professor G. J. CUNNINGHAM as treasurer, and Dr. D. A. H. PRATT as secretary. Further information can be obtained from Dr. D. A. H. PRATT, Research Division, Glaxo Laboratories, Ltd., Greenford, Middlesex.

Royal Society of Medicine Honorary Fellows

The following have been elected to Honorary Fellowship of the Society: Sir SAMUEL BEDSON, Sir STANFORD CADE, Professor D. E. CANNELL, Dr. G. B. DOWLING, Sir STEWART DUKE-ELDER, Mr. W. SAMPSON HANDLEY, Sir DAVID HENDERSON, Sir HAROLD HIMSWORTH, Sir HARRY JEPHCOTT, Dr. F. H. KRUSEN, and Sir HENRY SOUTTAR.

Faculty of Ophthalmologists

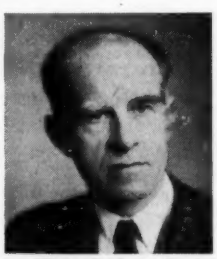
The following have been elected Officers of the Faculty for 1961–2: *president*, Professor G. I. SCOTT; *immediate past president*, Mr. E. G. MACKIE; *vice-presidents*, Mr. J. E. M. AYOUB, Mr. P. JAMESON EVANS; *honorary treasurer*, Mr. G. T. WILLOUGHBY CASHELL; *honorary secretary*, Mr. J. R. HUDSON.

Association of Police Surgeons of Great Britain

The following officers for the year 1961–2 have been re-elected: *president*, Dr. R. H. COOKE; *honorary treasurer*, Mr. G. B. MALONE LEE; *honorary secretary*, Dr. C. H. JOHNSON.

Melbourne Chair for Professor Verney

Professor E. B. VERNEY, F.R.S., Sheild professor of pharmacology at the University of Cambridge and Fellow of Downing College, has accepted a personal research chair, without formal teaching duties, for three years in Professor R. D. WRIGHT'S department of physiology at the University of Melbourne. He hopes to go out to Australia when he retires from his Cambridge chair at the end of September.



[*Walter Stoneman, London*

Professor Verney, who was born in 1894, was educated at Tonbridge School, Downing College, Cambridge, St. Bartholomew's Hospital, and Freiburg im Breisgau. He was appointed professor of pharmacology at University College, London, in 1926, and took up his Cambridge professorship in 1934. He was elected F.R.S. in 1936 for his work on urinary secretion and on the pituitary. During his stay in Australia he hopes to study experimentally the effects of adrenal hormones on the isolated canine kidney and on bronchomotor tone and pulmonary arterial pressure. He also hopes to work on problems connected with the release of the antidiuretic hormone and its action on electrolyte excretion.

Shortage of Nurses

West Middlesex Hospital, Isleworth, has had to close six wards, housing 170 of its 1,066 beds, because it is short of nurses. The hospital needs 134 student nurses to bring its nursing staff up to full strength.

"Journal de Médecine de Nantes"

The joint faculty of medicine and pharmacy and the university hospital centre of Nantes have published the first issue of their new quarterly *Journal de Médecine de Nantes*. Editorial inquiries should be sent to Professor AGRÉGÉ J. GUILLON (22 rue des Halles, Nantes, Loire-Atlantique, France) and subscription inquiries to La Librairie des Facultés de Médecine et de Pharmacie, 174 Boulevard Saint-Germain, Paris 6e, France. The overseas subscription rate is 25 NF a year.

New Equipment for Severely Disabled

A demonstration of writing and reading equipment for the severely disabled, organized by a subcommittee of the National Fund for Research into Poliomyelitis and Other Crippling Diseases, was held on May 31. A control was shown for an electric typewriter for the use of patients with total body paralysis—that is, with no limb, trunk, or head movement, but able to suck and blow gently and independently of any breathing through nose or through a tracheotomy. Such a patient, it was said, would soon be able to type quicker than the average person can write by hand. Also demonstrated was a multi-purpose switch, again for a patient with total body paralysis, enabling him to effect 48 functions (and eventually an indefinite number)—such as switching on the radio or T.V., calling the telephone exchange and obtaining a number, turning on a light, ringing a bell. The motivating device is based on the same principle as that for the typewriter. A microfilm projector for a disabled patient unable to turn the pages of an ordinary book was also shown. The first two devices are still in the prototype stage. The Fund's address is Vincent House, Vincent Square, London S.W.1.

Elderly Invalids' Fund

During 1960 the Fund's work expanded rapidly, and 185 elderly invalids were assisted, compared with 135 the year before. As an increasing number of applications are coming from outside London the Fund hopes to set up local committees in the main towns of Surrey, Kent, Essex, and Buckinghamshire. Assistance to invalids covered 3,000 patient-weeks, compared with 2,089 in 1959, and the number supported continuously throughout the year rose to 57, compared with 40 the year before. The year ended with a heavy deficit of £1,793. The Fund deplores the passing of elderly people from one charity to another, and asks whether organizations as a whole are in touch with each other as they should be. The Fund's address is 24 London Bridge Street, London S.E.1.

Safety Precautions in Non-ferrous Metal Industry

Requirements for the protection of workers engaged in the melting or founding of non-ferrous metals are proposed in the revised preliminary draft of the Non-ferrous Metals (Melting and Founding) Regulations issued by the Ministry of Labour. Copies of the draft regulations may be obtained from the Ministry's Safety, Health and Welfare Department (W.5), at 19 St. James's Square, London S.W.1. Any observations on these draft regulations should be made in writing to the Ministry of Labour, at that address, by August 31.

Wolfson Grant to University College, London

The Wolfson Foundation has made a grant of £200,000 to University College, London. It will be used to recondition and equip a building for the development of the Galton Laboratory and the Departments of Eugenics, Genetics, and Biometry.

"Family Doctor"

The June issue of *Family Doctor* has now been published and costs 1s. 6d. It contains articles on dreaming by Dr. F. R. C. CASSON; on allergic conditions due to cosmetics by Professor C. D. CALNAN; on smoking, personality, and lung cancer by Professor H. J. EYSENCK; on foreign bodies by Mr. D. F. N. HARRISON; and on colour blindness by Mr. J. H. DOBREE. There is also an article on the work of the College of General Practitioners.

Anniversaries

The National Institute for the Deaf was founded in the summer of 1911. It will mark its jubilee by a series of articles in its journal, *The Silent World*, describing the work of its various departments.

British Industrial Biological Research Association

The Research Association was formed in 1960, with the support of the Department of Scientific and Industrial Research, to carry out toxicological investigations on substances used in the processing and packaging of food and cosmetics, and a new biological research station for this purpose is currently being planned. Dr. L. GOLBERG, medical research director of Benger Laboratories, Ltd., has been appointed director of the Research Association, and will take up his appointment at the end of the year.

People in the News

Professor A. C. FRAZER, professor of medical biochemistry and pharmacology at Birmingham University, has been invited to become a member of the Agricultural Research Council.

Dr. C. MANDERS, Ph.D., has been appointed to the newly created post of scientific attaché to the British Embassy in Tokio to advise on scientific matters and report on Japanese scientific and technical developments in the civil field.

Dr. R. CONRAD, Ph.D., assistant director of the Medical Research Council's Applied Psychology Research Unit, Cambridge, has been appointed consultant in applied psychology to the Post Office for an initial period of two years.

Professor RAGNAR GRANIT, head of the neurology department, Nobel Institute, Karolinska Institute, Stockholm, has been awarded the Anders Jahre prize for 1961. The prize, given by a Norwegian shipowner, is worth £5,000.

COMING EVENTS

Institute of Dermatology.—Exhibition, June 1–29, by Dr. E. J. MOYNAHAN, "Biology of the Skin Surface," St. John's Hospital for Diseases of Skin, Lisle Street, Leicester Square, London W.C.2.

Birmingham Medical Exhibition.—June 12–16, Princes Hall, Broad Street, Birmingham. Details from the Organizer at that address.

West London Medico-Chirurgical Society.—Annual banquet, June 15, 7.30 p.m., restaurant, Zoological Society, Regent's Park, London N.W.1. Tickets (35s.) from Society's Honorary Secretaries, West London Hospital, Hammersmith, London W.6.

5th Oliver Bird Lecture.—Dr. A. S. PARKES, F.R.S., "The Biological Control of Conception," June 20, 5 p.m. See advertisement p. 54.

Sir Halley Stewart Trust Lecture.—Dr. R. A. BUTLER (Sir Halley Stewart Research Fellow, Royal College of Surgeons of England), "Some Problems of the Pharmacokinetics of Anaesthetics," June 22, 5.30 p.m., Lecture Theatre, Wright-Fleming Institute, St. Mary's Hospital, Praed Street, London W.2. Free, no tickets.

Central Council for Health Education.—Summer school in health education, "Education for Living," August 15–25, Neuadd Reichel, University College of North Wales, Bangor. Sir JOHN CHARLES, "Public Health Trends in Present-day Britain." Fee £24 4s. Details from C.C.H.E., Tavistock House North, Tavistock Square, London W.C.1. (EUSton 3341–5.)

Congress of International Society of Surgery and International Cardiovascular Society.—Dublin, September 2–9. Details from Mr. H. O'NEILL, 16 Harcourt Street, Dublin.

10th International Congress on Rheumatic Diseases.—Rome, September 4–7. Details from Professor C. B. BALLABIO, Clinica Medica Generale, 35 Via F. Sforza, Milan, Italy.

4th International Congress of Angiology.—Prague, September 4–9. Organized by Union Internationale d'Angéiologie of Paris. Main theme: "Metabolism of the Vascular Wall." Details from Professor Dr. ZDENEK REINIS, IVth Medical Clinic, Prague 2/499, Czechoslovakia.

University of Sheffield.—Refresher course for general practitioners, beginning September 25. See advertisement p. 54.

W.H.O., Food and Agriculture Organization of U.N., International Atomic Energy Agency.—International conference, "Uses of Radioisotopes in Animal Biology and the Medical Sciences," Mexico City, November 21–December 1. Details from sponsoring organizations.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, June 5

INSTITUTE OF DERMATOLOGY.—At British Institute of Radiology, (1) 4 p.m., Dr. L. Szur: Radiotherapy of Malignant Skin Conditions (II). (2) 5 p.m., Mr. I. Muir: Reconstructive Surgery and Malignant Disease.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. J. Sharp: Ankylosing and Rheumatoid Spondylitis.

Tuesday, June 6

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Professor R. S. Speirs: Role of Eosinophils in Inflammation.

MIDDLESEX HOSPITAL MEDICAL SCHOOL.—At Clinical Lecture Theatre (first-floor cross-piece), 4.15 p.m., Sanderson Wells Lecture by Sir William Ogg: Soil, Crop Nutrition, and Health.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute, 5 p.m., Mr. Frank Musgrove: Impressions of Obstetrics and Gynaecology in America.

UNIVERSITY COLLEGE LONDON: DEPARTMENT OF PHARMACOLOGY.—At Physiology Theatre, Gower Street, W.C., 5.30 p.m., public lecture by Dr. G. P. Lewis: Bradykinin—its Chemistry, Pharmacology, and Role in Physiological and Pathological Reactions.

Wednesday, June 7

BROOK GENERAL HOSPITAL, Shooters Hill, London S.E.—5.45 p.m., Dr. L. Morris: Cerebral Angiography.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. W. Riddell: World Distribution of Fungus Infections.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., open lecture by Dr. W. M. Macleod: Abnormal Transradiancy of One Lung.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Dr. I. Friedmann, Dr. D. A. Osborn, and Dr. A. L. Jeanes: clinical pathological conference.

MANCHESTER MEDICAL SOCIETY: SECTION OF GENERAL PRACTICE.—4 p.m., clinical meeting. Visit to Department of Clinical Pathology, Manchester Royal Infirmary.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. P. Wildy: Architecture of Viruses.

ROYAL FREE HOSPITAL, Gray's Inn Road, London W.C.—5.15 p.m., Sir Horace Smirk (Dunedin): Pathogenesis and Management of Hypertension.

Thursday, June 8

HONYMAN GILLESPIE LECTURES.—At Anatomy Theatre, University New Buildings, Teviot Place, Edinburgh, 5 p.m., Dr. J. A. Tulloch: Occurrence of Diabetes Mellitus in the Tropics.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. Raymond Daley: Arteritis.

ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5.15 p.m., Lord James: Education of the Scientist.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Hunterian Lecture by Professor I. Ranger: Study of the Functional Anatomy of the Diaphragm, with special reference to the Aetiology and Treatment of Oesophageal Hiatus Hernia.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. Desmond Curran: postgraduate demonstration in psychiatry.

Friday, June 9

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. N. C. Oswald and Mr. O. S. Tubbs: clinical demonstration.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—(1) 10 a.m., Mr. G. C. Tresidder: Some Urological Operations; (2) 4 p.m., Sir Horace Smirk: Hypertension—Treatment and Pathogenesis.

Saturday, June 10

CHILTERN MEDICAL SOCIETY.—(1) At High Wycombe Hospital, 4.30 for 5 p.m., annual oration. (2) At Bellhouse Hotel, Beaconsfield, 7.30 for 8 p.m., annual dinner.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Davies.—On May 3, 1961, at St. David's Hospital, Cardiff, Glam, to Rhiannon, wife of Dr. John L. Davies, a brother for Peter and Patricia—Jonathan.

Krikler.—On May 17, 1961, at 5 Chelmsford Road, Avondale, Salisbury, Southern Rhodesia, to Hanneliese (formerly Winterstein), wife of Dennis Michael Krikler, M.B., M.R.C.P., a son—Paul Alan.

DEATHS

Abercrombie.—On May 14, 1961, at the Royal Hospital, Sheffield, Yorks, Rodolph George Abercrombie, M.D., D.T.M.

Agnew.—On May 11, 1961, Alexander Percy Agnew, M.B., C.M., aged 91.

Browne.—On May 18, 1961, at her home, Bournstream, Wotton-under-Edge, Glos, Enid Marjorie Moore Browne, M.R.C.S., L.R.C.P.

Chester-Williams.—On May 12, 1961, at his home, 24 North Park Road, Bradford, Yorks, Frank Edward Chester-Williams, M.R.C.S., L.R.C.P., F.F.R.

Coles.—On May 12, 1961, at Brown Leaves, 4 Fairfield Road, Uxbridge, Middx, Bennett Alsop Coles, M.R.C.S., L.R.C.P.

Collins.—On May 15, 1961, at Broadlands, 35 Thorpe Road, Peterborough, John Norton Collins, M.D., aged 92.

Davies.—On May 17, 1961, at the Cambridge Military Hospital, Aldershot, Hants, Ronald Martyn Davies, M.B., B.S., Lieutenant-Colonel, R.A.M.C., retired, of Rushy Close, Dogmersfield, Hants, aged 78.

Greenwood-Penny.—On May 16, 1961, at St. Michael's Hospital, Hayle, Cornwall, Sydney Augustus Greenwood-Penny, M.R.C.S., L.R.C.P., of Trewynn, Marazion, Cornwall.

Hutton.—On May 11, 1961, the result of a road accident, Samuel King Hutton, M.D., L.H.D., D.Obst.R.C.O.G.

Twort.—On May 7, 1961, at Frimley Hospital, Frimley, Aldershot, Hants, John Ferdinand Twort, M.R.C.S., L.R.C.S., of Hurstwood, Camberley, Surrey, aged 80.

Wharton.—On May 9, 1961, Edgar Wharton, M.B., Ch.B., of The Orchard, Thorncliffe Drive, Cheltenham, Glos, aged 80.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Treatment of Snake-bite, Anthrax, and Botulism

Q.—*Where may emergency supplies of therapeutic and prophylactic agents for snake-bite, anthrax, and botulism be obtained in England and Wales?*

A.—Memorandum H.M.(58)66 issued by the Ministry of Health lists the following centres as holding supplies of these agents. A 24-hour service is maintained at each centre.

Region 1: Newcastle.—The Pathological Laboratory, Cumberland Infirmary, Carlisle (anthrax antiserum and snake-bite antivenom only) (Carlisle 22332); The Dispensary, Newcastle General Hospital (Newcastle 38811).

Region 2: Leeds.—Castle Hill Hospital, Cottingham, Hull (Cottingham 47371); Seacroft Hospital, York Road, Leeds (Leeds 648164).

Region 3: Sheffield.—Nottingham City Hospital, Hucknall Road, Nottingham (Nottingham 63361).

Region 4: East Anglia.—Regional Transfusion Centre, Brooklands Avenue, Cambridge, Monday–Friday, 8.30 a.m.–5.30 p.m., and Saturday, 8.30 a.m.–12.30 p.m. (Cambridge 56912; all other times Cambridge 56913).

Region 5: North-west Metropolitan.—Edgware General Hospital (Edgware 2381).

Region 6: North-east Metropolitan.—North Middlesex Hospital, N.18: Day—Chief Pathologist, Night—Resident Pathologist (Edmonton 3071).

Region 7: South-east Metropolitan.—South London Transfusion Centre, South-east Sub-depot, David Salomon House, Southborough, near Tonbridge: day service (Southborough 1480); night service (Maidstone 4463 and 4660).

Region 8: South-west Metropolitan.—South London Transfusion Centre, Stanley Road, Sutton, Surrey (Vigilant 8221); Royal Portsmouth Hospital, Commercial Road, Portsmouth (snake-bite antivenom only) (Portsmouth 22281); *The Dispensary, Royal South Hants and Southampton Hospital (botulinus antitoxin and snake-bite antivenom only) (Southampton 26211); Royal Victoria Hospital, Shelley Road, Bournemouth (snake-bite antivenom only) (Boscombe 35201).

Region 9: Oxford.—Northampton General Hospital (Northampton 4680); Royal Berkshire Hospital, Reading (Reading 81721).

Region 10: South-western.—Ham Green Hospital, Bristol (Pill 2165); Pathological Department, Royal Devon and Exeter Hospital, Exeter (Exeter 73519; Exeter 72261 when laboratory closed); Scott Isolation Hospital, Plymouth (Plymouth 64311 and 61437); Pathological Department, Royal Cornwall Infirmary, Truro (Truro 3029).

Region 11: Wales.—Cardiff Isolation Hospital, Cardiff (Cardiff 21466); West Wales General Hospital, Glangwilli, Carmarthen (botulinus antitoxin and snake-bite antivenom only) (Carmarthen 6733); Aberystwyth General Hospital (botulinus antitoxin and snake-bite antivenom only) (Aberystwyth 374); Caernarvon and Anglesey General Hospital, Bangor (botulinus antitoxin and snake-bite antivenom only) (Bangor 3321–5); Maelor General Hospital, Wrexham (Wrexham 3512).

Region 12: Birmingham.—The Dispensary, Selly Oak Hospital, Birmingham (Selly Oak 1361).

Region 13: Manchester.—The Dispensary, Manchester Royal Infirmary (Ardwick 3300).

Region 14: Liverpool.—Fazakerley Hospital, Longmoor Lane, Liverpool 9 (Aintree 2342).

Anthrax antiserum for use prophylactically

Antiserum required for persons exposed to infection may also be obtained in 10-ml. containers during the day-time from the following centres:

Region 1: Newcastle.—Public Health Laboratory, Institute of Pathology, General Hospital, Westgate Road, Newcastle 4 (Newcastle 38811).

Region 2: Leeds.—Public Health Laboratory, 16/18 Edmund Street, Bradford 5 (Bradford 24314); Public Health Laboratory, 184 High Street, Kingston-upon-Hull (Hull Central 35371).

Region 5: North-west Metropolitan.—Central Public Health laboratory, Colindale Avenue, London N.W.9 (Colindale 7041).

Region 9: Oxford.—Public Health Laboratory, General Hospital, Northampton (Northampton 347).

Region 10: South-western.—Public Health Laboratory, Musgrove Park Hospital, Taunton (Taunton 5753).

Region 11: Wales.—Public Health Laboratory, Institute of Preventive Medicine, The Parade, Cardiff (Cardiff 29110 and 23967).

Region 12: Birmingham.—Public Health Laboratory, Royal Infirmary, Worcester (Worcester 5238/9).

Region 14: Liverpool.—Public Health Laboratory, 126 Mount Pleasant, Liverpool (Royal 3636).

*This hospital carries snake-bite antivenin not only against native snakes but against tropical snakes which may be imported with cargoes arriving at the docks.

Tin for Staphylococcal Infections

Q.—*Are compounds of tin effective in the treatment of staphylococcal infections? If so, what is their mode of action?*

A.—In the days before effective antibacterial drugs were available compounds of tin were frequently recommended for the treatment of staphylococcal infections, particularly furunculosis. Their use for this purpose was based on a French observation made during the first world war which suggested that tin had a specific antagonistic effect against the staphylococcus. This was not confirmed, and there was never any definite clinical proof of the value of preparations of tin in staphylococcal infections. Tin and its salts have no place in modern therapeutics.

Safety Straps in Cars

Q.—*What is the most suitable type of safety strap for car occupants?*

A.—There are many factors involved in the choice of safety belts and harnesses. Some types may be expected to give more protection than others in an accident—e.g., a complete harness is likely to be more effective than a lap strap. However, the lap strap is more convenient to use than the complete harness, and might be more likely to be used. Some installations also cause some obstruction to the passengers in the rear seat, and some cars are not suitable for attaching some of the equipment. For example, the cross-over type of strap, one end of which is attached to the door pillar, cannot be used if there is no door pillar or if the interior light is situated at this point. Finally, there is the question of price, which is probably an important factor. The Road Research Laboratory recommend the full harness, the cross-over plus lap strap, or the cross-over type for drivers and front-seat passengers; and, of course, it is important that the equipment complies with the British Standard, B.S.3254. Useful articles on safety belts and harnesses have appeared in a recent issue of *Shoppers Guide* (No. 17, 1960, pp. 7–13).

Enlarged Clitoris

Q.—*A woman aged 60 has an enlarged clitoris of about ¾ in. (19.1 mm.) long. There is no evidence of hormonal imbalance, and the patient is not sure how long the clitoris has been enlarged. She had a short course of tablets containing methyltestosterone (3.6 mg.) and ethinyloestradiol (0.0044 mg.) for menopausal symptoms at the age of 49–51. She is married and has a grown-up daughter. What size of clitoris should be regarded as abnormal, and can this patient be just reassured?*

A.—There is not an absolute standard of size for the normal clitoris—it varies with individuals. A length of ¾ in., presumably measured without reckoning the subcutaneous part of the phallus, does, however, suggest hypertrophy. Abnormality is perhaps further indicated by the fact that the patient is aware of the organ; this may mean that it is larger than it was previously. The tablets she has taken contain an appreciable amount of androgen and could cause enlargement of the clitoris. Such an effect, however, would appear immediately and not eight or nine

years later, as in this case. Other possibilities should therefore be entertained, and particularly a small androgenic tumour of the ovary, such as an arrhenoblastoma or a hilar cell tumour. Such a tumour may be so small as not to be obvious on bimanual examination. Indeed, a hilar cell tumour can pass unrecognized at laparotomy unless the ovary is sectioned. It may be added that these tumours do not always produce all the signs of virilism such as hirsutism and voice changes. Their effects sometimes show only in one target organ, so they may still be present even though the only clinical evidence is hypertrophy of the clitoris. Nor do they usually result in an increased excretion of 17-ketosteroids in the urine. In this respect they differ from an androgenic tumour of the adrenal, the presence of which in this case could be virtually excluded by the finding of a normal level of these excretion products.

Digitalis with Quinidine

Q.—*Can quinidine be given at the same time as digitalis? An elderly lady had a coronary thrombosis a few years ago, and was subsequently digitalized for mild cardiac failure. The digitalis has been continued, but she is now having prolonged attacks of paroxysmal tachycardia.*

A.—Quinidine can certainly be given at the same time as digitalis. Indeed, if it is desired to convert atrial fibrillation to sinus rhythm with quinidine it is advisable for the patient to be digitalized[1] to prevent an increase in ventricular rate due to diminution of atrioventricular block resulting from a reduction in atrial rate. It is, however, inadvisable to give full doses of digitalis and full doses of quinidine at the same time.

In the case quoted it is presumably desired to give quinidine in prophylactic dosage of 6–12 gr. (0.4–0.8 g.) daily to prevent attacks of paroxysmal tachycardia. Provided that the patient is not sensitive to quinidine there is no objection to its administration in this way. However, when paroxysmal tachycardia occurs in a patient who is already having digitalis, the possibility of digitalis intoxication producing the tachycardia must be considered. It is not possible to say whether this might be the cause in the patient quoted without full clinical and cardiographic details.

REFERENCE

1 Wood, P., *Diseases of the Heart and Circulation*, 2nd ed., 1956. Eyre and Spottiswoode, London.

Fish-poisoning in the Pacific

Q.—*Recently there have been two fatal cases of fish-poisoning in Tonga, and the symptoms appeared to correspond with those of organo-phosphorus poisoning. (1) Is the pharmacology of fish-poisoning the same as that of poisoning by the organo-phosphorus compounds? (2) Would the treatment for organo-phosphorus poisoning be suitable for fish-poisoning?*

A.—Poisoning through eating fresh fish in the Pacific was first described in the English literature by Cook.[1] It appears to occur fairly commonly in the tropical part of the Pacific, and most of the islands, with the reputed exceptions of Sikiana and Tonga, have poisonous fish.[2] It would now seem that these fish extend to Tonga. Very many different species of fish have been found to be poisonous but not all fish of the same species are poisonous, and there can be seasonal variations in their toxicity. The only certain way of diagnosing poisonous fish is by biological assay, the recommended test species being the mongoose.[3] The variety of species involved and the frequent relation between the toxicity of the fish and the precise area where they have been caught has led people to think that the toxin is derived from something in the diet of the fish.[3,4] A possible exception is the puffer fish, whose toxin may be endogenous.

The symptoms of poisoning seem to be much the same wherever they occur. Muscle and joint pains, headache, excessive salivation, vomiting, weakness, and muscular incoordination occur, leading in fatal cases to paralysis and coma. There is loss of the knee and ankle reflexes, and in non-fatal cases paraesthesiae lasting up to several weeks seem to be a common feature.

The treatment of the condition has been largely symptomatic. Castor-oil has been given at the outset, atropine will relieve the salivation, and promethazine hydrochloride will diminish the paraesthesiae. The postulated resemblance to organo-phosphorus poisoning is only very superficial, and these toxins are not acetylcholinesterase inhibitors.[5] Their effect on neuromuscular transmission is thought to be due to inhibition of the release of acetylcholine.[6] Consequently the treatment recommended for organo-phosphorus poisoning would not be suitable for these cases. The extremely high toxicity of these substances has aroused the interest of pharmacologists in many centres, and their mode of action is being strenuously investigated. It is to be hoped that a rational plan of therapy will emerge from these studies.

REFERENCES

1 Cook, J. *A Voyage towards the South Pole and Round the World (In the "Resolution" and "Adventure") in 1772-5*, 1777.
2 Mills, A. R., *J. trop. Med. Hyg.*, 1956, **59**, 99.
3 Banner, A. H., and Burroughs, H., *Proc. Soc. exp. Biol. (N.Y.)*, 1958, **98**, 776.
4 Randall, J. E., *Bull. Mar. Sci. Gulf and Caribbean*, 1958, **8**, 236.
5 Dettbarn, W. D., Higman, H., Rosenberg, P., and Nachmansohn, D., *Science*, 1960, **132**, 300.
6 Fleisher, J. H., Killos, P. J., and Harrison, C. S., *Fed. Proc.*, 1960, **19**, 264.

Withdrawing C.S.F. from Spitz–Holter Valve

Q.—*Is it possible to withdraw cerebrospinal fluid from the bulbous part of a Spitz–Holter valve, and are there any particular dangers in such a procedure?*

A.—The Spitz–Holter valve used for the treatment of hydrocephalus consists of two cone-shaped valves partly encased in metal tubes and joined to one another by a short silicone rubber tube. It is this central portion which is referred to in the question. Although it is possible to obtain a sample of cerebrospinal fluid by aspiration from this part, there is considerable risk of damage to the apparatus, which is both delicate and costly. The silicone rubber tube splits readily, and after insertion of a needle will leak cerebrospinal fluid through the puncture, even at the low pressure at which the valve operates. Furthermore, there is a chance of damaging the valve mechanism with the point of a needle. These risks are greater than those of obtaining a sample from the lateral ventricle, which can usually be punctured through the coronal suture in these patients, when the lumbar route is not available and the fontanelle is closed. Cisternal puncture is not advised in cases of myelomeningocele.

Correction.—We regret a misprint in Dr. A. M. Foxe's letter on "Tumours in Children." Lord Moynihan's phrase was "the *adnormal* case," not "abnormal case."

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